

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL)
PRODUCTS LIABILITY LITIGATION

MDL NO. 2740

SECTION “H” (5)

THIS DOCUMENT RELATES TO:
ALL CASES

**DEFENDANTS’ OPPOSITION TO PLAINTIFFS’ MOTION FOR LEAVE TO FILE
THIRD AMENDED MASTER LONG-FORM COMPLAINT AND JURY DEMAND**

The Court should deny Plaintiffs’ Motion to file a Third Amended Master Long-Form Complaint and Jury Demand (Rec. Doc. 8334, “Motion”). Contrary to statements made in Plaintiffs’ Motion, the proposed Third Amended Complaint does not merely “provide[] more details about the actions and inactions that form the bases of already-existing causes of action.” (Rec Doc. 8334-at 1). Rather, it attempts to substantively alter and broaden Plaintiffs’ definition of their alleged injuries and to skirt this Court’s rulings on plainly time-barred lawsuits.

- First, in their proposed Third Amended Master Complaint, Plaintiffs fundamentally change the definition of their injury from occurring six-months following chemotherapy to lacking any “single definition,” sometimes occurring “between twelve to twenty-four months following chemotherapy treatment.”¹
- Second, Plaintiffs added argumentative allegations that Defendants hid the alleged risk of permanent hair loss with Taxotere from the medical community.²

Plaintiffs have offered no credible justification or explanation for seeking a fourth iteration of their Master Complaint—having been granted two prior amendments—after several rounds of

¹ See Exhibit A (Redline Comparison of Plaintiffs’ Second Amended Master Complaint and proposed Third Amended Master Complaint) at ¶¶ 193–198.

² See *id.* at ¶¶ 154, 158, 164, 167, 175, and 233–42.

dispositive briefing on their Second Amended Master Complaint, statute-of-limitations rulings from this Court, a first trial through jury verdict, and the close of fact discovery and amidst expert discovery for the second trial. Rather than narrow Plaintiffs' claims based on the work the parties and Court have done over the last three years, Plaintiffs seek to use the Master Complaint—a tool for streamlining pleadings early in an MDL—to expand their claims universally and to make them not only more ambiguous, but also contrary to their own sworn Plaintiff Fact Sheets, deposition testimony, and expert opinions.

If Plaintiffs are granted leave to amend, the Defendants will be entitled to another round of Rule 12 briefing. More than 11,000 cases incorporating the earlier Master Complaint in the operative Short Form Complaint—many explicitly adopting a six-month definition of each Plaintiff's injury—will need to be amended and refiled. Allowing Plaintiffs to change their injury definition at this late date will undo and reopen years' worth of expert work, based solely on a tactical, not factual, change in circumstances. Plaintiffs cite no authority that would permit them to modify and broaden their claims or an MDL in this way, much less at this late stage. To the contrary, relevant case law confirms that motions to amend the pleadings should be denied where, as here, amendment is unduly delayed and would be prejudicial to Defendants. Plaintiffs' request is contrary to the objectives of "the just and efficient conduct of" this MDL, 28 U.S.C. § 1407(a), and their Motion should be denied.

BACKGROUND

The Master Complaint was intended to identify inventory-wide legal issues and factual allegations at the outset of the litigation. *See* Exhibit B, Hr'g Tr. at 33:10–21 (Nov. 10, 2016) (Engelhardt, J., presiding) (Judge Engelhardt explained that a Master Complaint is used to "tee everything up" and specifically instructed that a Master Complaint should be addressed "early on"

by liaison counsel). Counsel identified Plaintiffs’ definition of their alleged injury as a key issue as long as three years ago, explaining that “how []we define” Plaintiffs’ injury “will [] have a significant impact on how we are able to . . . collectively evaluate our cases[.]” *See id.* at 45:16–46:2. Since Plaintiffs’ original Master Complaint filed March 31, 2017, Plaintiffs have relied on a single definition of each Plaintiff’s alleged injury: “an absence of or incomplete hair regrowth **six months** beyond the completion of chemotherapy.” *See* Rec. Docs. 312 at ¶ 181 (Plfs.’ Master Long Form Complaint), 689 at ¶ 180 (Plfs.’ First Amended Master Long Form Complaint), 4407 at ¶ 181 (Plfs.’ Second Amended Master Long Form Complaint) (emphasis added).

The Court ordered Plaintiffs to make any necessary amendments to their pleadings more than a year before the first trial.³ Magistrate Judge North utilized Plaintiffs’ definition of their alleged injury in resolving discovery disputes on Plaintiffs’ serial 30(b)(6) corporate representative depositions of Sanofi. Rec. Doc. 3473 at 2 (Judge North Minute Entry re Hearing on Defs.’ Mot. for a Protective Order) (for the purposes of the deposition, “the term ‘persistent alopecia’ shall mean that which remained six months after chemotherapy ended and without resolution.”). And this Court cited Plaintiffs’ six-month definition in ruling on summary judgment motions based on the statute of limitations. *See* Rec. Doc. 7571 (Order and Reasons on Motion for Summary Judgment Based on Statute of Limitations Defenses) at 2 (“According to the Master Complaint, Plaintiffs’ injuries—disfiguring permanent alopecia—manifested six months after the completion of chemotherapy.”).

³ *See* Rec. Doc. 935 (CMO 8) (“Amendments to pleadings, third-party actions, cross-claims and counter-claims shall be filed no later than June 29, 2018, in accordance with the Federal Rules of Civil Procedure and Local Rule 7.6.”). Although CMO 8 was superseded by Rec. Doc. 3064 (CMO 14) shortly before the June 2018 amendment deadline, it remains obvious that the time for Amendments to the Master Complaint has long since passed.

Only now, after the Court granted summary judgment on statute-of-limitations grounds in the *Johnson* and *Francis* matters, do Plaintiffs seek to redefine their alleged injury from accruing six months after chemotherapy to occurring six or twelve or twenty-four or more months after chemotherapy. *See* Exhibit C, Plfs.’ Proposed Third Amended Master Complaint at ¶ 194 (now alleging there is “no single definition” for Plaintiffs’ alleged injury and the “scientific literature has variously referred to Permanent Chemotherapy Induced Alopecia as occurring between twelve to twenty-four months following chemotherapy treatment.”). Plaintiffs also seek to add allegations that Defendants allegedly hid from the medical community and patients that Taxotere allegedly can cause permanent hair loss. *See id.* at ¶¶ 168, 233–242.

Not only are several of these allegations based on arguments excluded from the first Bellwether trial (Rec. Doc. 8201 at 5–6 (Order and Reasons precluding evidence or argument regarding foreign labeling and regulatory actions or of third party advocacy or communication groups)), Plaintiffs’ fraudulent-concealment allegations have no place in the Master Complaint. *See* Exhibit D, Hr’g Tr. at 23:4–7 (Aug. 30, 2017) (Engelhardt. J., presiding) (Judge Engelhardt explained that while Plaintiffs’ fraud based claims would not be dismissed, “specific allegations, particularly with respect to any allegations of fraud, should be perfected within the short form complaints filed in the individual member cases.”).

Plaintiffs’ motivation for these amendments is transparent. Without a clear definition of when their injury manifested, and with padded allegations of fraudulent concealment, Plaintiffs hope to muddy the record and avoid statute-of-limitations dismissals. Yet it is undisputed (i) when these Plaintiffs lost their hair, and (ii) that thousands of Plaintiffs have identified the date of their hair loss, or when their hair failed to regrow completely within six months of chemotherapy ending, as the onset date of their injury. So regardless of what allegations Plaintiffs include in the

Master Complaint, nothing will change the fact that thousands of Plaintiffs have filed lawsuits years out-of-time. What will happen with an amendment, instead, is administrative and procedural upheaval. Plaintiff's Motion should be denied.

LEGAL STANDARD

While Rule 15 provides that “leave to amend a pleading should be given freely ... when justice so requires,” the “generous standard set forth in Rule 15(a) is tempered by the necessary power of a district court to manage a case.” *See Lackey v. SDT Waste & Debris Servs., LLC*, No. 11-cv-1087, 2014 WL 2861819, at *2 (E.D. La. June 24, 2014) (quoting *Schiller v. Physicians Res. Grp. Inc.*, 342 F.3d 563, 566 (5th Cir. 2003) (internal quotation marks omitted)). The Supreme Court has identified five factors to consider when assessing whether to deny leave to amend a complaint: “undue delay, bad faith or dilatory motive on the part of the movant, repeated failure to cure deficiencies by amendments previously allowed, undue prejudice to the opposing party by virtue of the allowance of the amendment, [and] futility of the amendment[.]” *Rosenzweig v. Azurix Corp.*, 332 F.3d 854, 864 (5th Cir. 2003) (quoting *Foman v. Davis*, 371 U.S. 178 (1962)). All relevant factors favor denying Plaintiffs’ Motion to Amend.

I. Granting Plaintiffs’ Motion to Amend will Unduly Prejudice Defendants.

A defendant is unduly prejudiced by granting leave to amend if the changes to the complaint would require additional discovery and the defendant to prepare a different defense. *Smith v. EMC Corp.*, 393 F.3d 590, 596 (5th Cir. 2004); *Parish v. Frazier*, 195 F.3d 761, 764 (5th Cir. 1999) (defendant unduly prejudiced by plaintiff’s attempt to broaden the issues, which would require additional discovery and another motion for summary judgment); *Pharr v. Wille*, No. 1:14-cv-762, 2016 WL 1448886, at *2 (W.D. Tex. Apr. 12, 2016) (denying motion to amend where the

case had entered the summary judgment stage because it would “fundamentally alter the course of [the] litigation”). Here, both would be required if Plaintiffs are granted leave to amend.

First, fact and expert discovery thus far has been conducted using Plaintiffs’ definition that they were injured no later than six months after finishing chemotherapy—including discovery in trial pool cases and with respect to all Plaintiff Trial I Expert Reports, all Defense Trial I Expert Reports, and *even all Plaintiff Trial II Expert Reports most recently produced on October 21, 2019*. See, e.g., Exhibit E, Tosti October 21, 2019 Report at 14, 16 (reviewing articles where “[c]ases of alopecia lasting more than 6 months after the end of chemotherapy” were reported, which is consistent with her prior deposition testimony that in the dermatological community, “permanent alopecia, by definition, is alopecia that persists at least six months after the end of chemotherapy,” Exhibit F, Tosti Dep. Vol. I at 207:21–24); Exhibit G, Feigal October 21, 2019 Report at 36 (defining PCIA as “an absence of or incomplete hair regrowth 6 months beyond completion of chemotherapy”); Exhibit H, Plunkett October 21, 2019 Report at ¶ 32 (stating that the medical literature generally recognizes permanent, irreversible alopecia as “hair that fails to regrow or substantially regrow at least by six months after treatment has ended.”); Exhibit I, Kessler October 21, 2019 Supplemental Report at ¶ 1 (incorporating by reference Dr. Kessler’s November 6, 2018 Report, which recognizes that “the medical literature has generally defined [irreversible alopecia] as the ‘complete loss of growth or partial regrowth at least 6 months after chemotherapy.’” See Exhibit J, Kessler November 6, 2018 Report at ¶ 81).⁴ That is, for Trial II,

⁴ See also Defense Expert Reports produced for Trial I: Exhibit K, Glaspy December 14, 2018 Report at 26 (explaining that the results of TAX316 do not indicate whether Taxotere causes *permanent* alopecia under Plaintiffs’ definition because “there is no documentary evidence to support any claim that [the majority of TAX316 patients reporting ‘ongoing’ alopecia] had alopecia more than six months after chemotherapy.”); Exhibit L, Arrowsmith December 31, 2018 Report at 48–49 (same); Exhibit M, Victoria December 28, 2018 Report at 49 n.191 (“It is my

not even a month ago, Plaintiffs’ experts all again proffered and relied on the same definition of permanent alopecia as Plaintiffs’ earlier Master Complaint. And this was after Plaintiffs had moved to amend their allegations to change the definition of their alleged injury from manifesting six-months after chemotherapy to lacking “any single definition.” *See* Exhibit C at ¶ 194. Defendants’ expert reports are now due in less than one month, and there is no time for Defendants’ experts to address Plaintiffs’ new injury definition. *See* Rec. Doc. 7416 (CMO 14D).⁵

Likewise, all case-specific discovery in the more than 30 cases that have been selected and worked up as potential trial cases has thus far proceeded under Plaintiffs’ “six months” definition of permanent alopecia. The deadline for fact discovery for Trial II has already passed, and Trial III discovery is well-underway, with selected cases proceeding into the next discovery phase. *See* Rec. Doc. 8430. All Trial I, II, and III Plaintiffs have been deposed under the theory that their alleged injury manifested six months after they finished chemotherapy. *See, e.g.*, Exhibit N, Thibodeaux Dep. Vol. I 276:3–6, 278:15–279:7 (testifying that by 2010, six months after completing chemotherapy, she was not seeing any more improvements to her hair regrowth); Exhibit O, Thibodeaux Dep. Vol. II 394:20–23 (same); Exhibit P, Thibodeaux Twelfth Amended Plaintiff Fact Sheet (“PFS”) at § VI.5 (defining her injury as “[s]ignificant thinning of the hair on [her] head after six (6) months of discontinuing Taxotere or Docetaxel treatment[.]”); Exhibit Q, Crayton Fifth Amended PFS at § VI.5 (same); Exhibit R, Wanda Stewart Third Amended PFS at § VI.5 (same); Exhibit S, Alice Hughes Third Amended PFS at § VI.5 (defining her injury as “[n]o

understanding that the Court defined ‘persistent alopecia’ for purposes of the Kopreski depositions as alopecia ‘that which remains six months after chemotherapy ended without resolution.’”).

⁵ The parties have agreed to extend the deadline for all Trial II Defendant Expert Reports, excluding pathologists and dermatologists, until December 9, 2019. Defendants’ pathologists’ and dermatologists’ expert reports are due December 16, 2019.

hair growth on [her] head or body after six (6) months of discontinuing Taxotere or Docetaxel treatment,” and identifying her injury as beginning August 2012, six months after she completed chemotherapy treatment in February 2012).

Similarly, significant MDL-wide discovery has been conducted using Plaintiffs’ six-month definition. For example, Plaintiffs deposed Sanofi’s 30(b)(6) witness, Dr. Michael Kopreski, for six days over 25 hours, all under Judge North’s Order that, for the purposes of the deposition, “the term ‘persistent alopecia’ shall mean that which remained six months after chemotherapy ended and without resolution.” Rec. Doc. 3473 at 2 (Judge North Minute Entry re Hearing on Defs.’ Mot. for a Protective Order). In those depositions, Plaintiffs asked Dr. Kopreski whether patients in scores of adverse event reports did or did not have “persistent alopecia” depending on whether there was evidence that hair had not regrown six months after chemotherapy had ended. That was the examination that Plaintiffs conducted; that was the definition that Plaintiffs employed to include or exclude adverse event reports. Both Plaintiff and Sanofi then introduced Dr. Kopreski’s testimony during the *Earnest* trial. *See, e.g.*, Exhibit T, Trial Tr. at 1915: 20–1916:7. Plaintiffs’ attempt to now change their definition of permanent alopecia would prejudice Sanofi, who prepared its witnesses and proffered its corporate position on issues based on Plaintiffs’ six-month definition. Whether and how Plaintiffs’ purported new definition of their injury would impact Dr. Kopreski’s testimony would undoubtedly become a subject of new and time-consuming discovery that would unfairly delay these proceedings.

Finally, Plaintiffs’ six-month defined injury was the only injury alleged in the first trial, where Plaintiff Earnest’s experts repeatedly asserted that permanent chemotherapy-induced alopecia is defined as incomplete hair regrowth six months beyond completion of chemotherapy. *See* Exhibit T, Trial Tr. at 986:10–14 (Dr. Tosti testified that the “classical diagnosis” of permanent

chemotherapy-induced alopecia is “incomplete hair regrowth six months after the end of chemotherapy.”); *id.* at 321:8–17 (Dr. Kessler explained the difference between “reversible” hair loss associated with chemotherapy and permanent hair loss caused by chemotherapy as whether the hair regrows within “three or six months.”); *id.* at Trial Tr. 432:4–20 (Dr. Kessler agreed that “six months with complete loss of growth or partial regrowth” is a “reasonable period of time” for defining “irreversible alopecia.”); *id.* at 644:21–25 (Dr. Madigan testified that he verified that the patients in the TAX316 clinical study with “permanent hair loss” were followed for at least six months).

If Plaintiffs are permitted to file a fourth Master Complaint, the current trial schedules cannot proceed. Defendants will be entitled to consider another round of Rule 12 briefing. Fact and expert discovery will need to be reopened so that Defendants can explore Plaintiffs’ new definition of their alleged injury, which is different than what Plaintiffs’ experts have opined about to date. Similarly, Defendants will need to explore whether to offer any new or additional expert opinions or clinical trial data analysis under Plaintiffs’ new definition. At the very least, Defendants’ current experts will need additional time to evaluate Plaintiffs’ injury and claims under this new definition, and to evaluate re-conducted fact discovery. Courts have denied motions to amend where, as here, it would “impose[] additional discovery cost” and potentially require “another round of dispositive motions.” *Squyres v. Heico Companies, L.L.C.*, 782 F.3d 224, 238–39 (5th Cir. 2015); *see also Smith*, 393 F.3d at 596 (“A defendant is prejudiced if an added claim would require the defendant to reopen discovery and prepare a defense for a claim different from the [one] ... that was before the court.”) (internal quotation marks and citation omitted); *Parish*, 195 F.3d at 764. Where, as here, “the amendments would ... affect the orderly progress of the MDL proceeding,” including by “open[ing] the door to at least some additional

discovery” in cases worked up for trial, amendments “would cause undue prejudice” and leave to amend should be denied. *In re Syngenta AG MIR 162 Corn Litig.*, No. 14-md-2591, 2016 WL 4705620, at *3 (D. Kan. Sept. 8, 2018).

If Plaintiffs were permitted to amend, Defendants also would need time to address proposed new allegations that Defendants fraudulently concealed information from the medical community and consumers. Discovery of Sanofi closed nearly a year ago, on December 15, 2018. Rec. Doc. 762 at 7 (CMO 5) (“general liability fact discovery shall be completed by December 15, 2018”). Sanofi is currently preparing expert reports based on the existing claims and record for deadlines in just a few weeks. General company discovery involving the 505(b)(2) Defendants Sandoz, Hospira, and Accord is in its late stages, with numerous 30(b)(6) and company witness depositions already completed. *See* Rec. Doc. 915 (CMO 7). Permitting Plaintiffs to broaden their claims and raise new allegations at this stage—more than two years after filing their original Master Complaint and well into the litigation—would unduly prejudice Defendants and necessarily delay the trial schedule. That Plaintiffs purport to derive their new allegations from documents produced by Sanofi does not avoid the prejudice since Sanofi and the other Defendants “had no reason to anticipate that [they] would need to defend allegations ... other than those that survived the motion to dismiss.” *In re Syngenta*, 2016 WL 4705620, at *3.

II. There is No Justification for Plaintiffs’ Delay.

The Court also should deny Plaintiffs’ attempt to amend their Master Complaint because the delay is not excusable. “Although Rule 15(a) does not impose a time limit ‘for permissive amendment, at some point, time delay on the part of a plaintiff can be procedurally fatal.’” *Smith*, 393 F.3d at 595 (quoting *Whitaker v. City of Houston*, 963 F.2d 831, 836 (5th Cir. 1992)). “In

such a situation, the plaintiff bears the burden of showing the delay to be ‘due to oversight, inadvertence, or excusable neglect.’” *Id.*

Defendants first raised their statute-of-limitations defense in dispositive motion practice on May 26, 2017. Rec. Doc. 494-1 (Defs.’ Mem. in Support of Their Mot. to Dismiss). Deferring that motion, the Court was inclined to work up the first round of trial pool cases before addressing the issue of broader disposition. *See* Rec. Doc. 1034 (Order and Reasons on Defs.’ Mot. to Dismiss Claims Barred by the Applicable Statute of Limitations); *see also* Exhibit U, Hr’g Tr. at 25:8–18 (Oct. 27, 2017) (Engelhardt, J., presiding) (the Court explained that it had denied Defendants’ omnibus statute of limitations motions without prejudice, believing it would be “more prudent to take the issues up after the first round of discovery,” and “it’s something that we’ll certainly revisit.”). Plaintiffs had more than a year after that ruling and before Trial I expert reports were due to amend their Master Complaint, but they failed to do so. In fact, Plaintiffs amended their Master Complaint on July 25, 2017, and again on September 27, 2018, but they never changed the definition of their alleged injury nor added the factual allegations they seek to include now. *See* Rec. Docs. 689, 4407 (First and Second Amended Master Complaints). Plaintiffs offer no explanation or excuse for their delay, asserting only that they learned new details “through discovery.” Rec. Doc. 8334-1 (Motion) at 1. But fact discovery of Sanofi closed last December. If Plaintiffs believed they needed more time to amend their Master Complaint “based on the produced documents, they should ... have brought the matter to the Court’s attention in light of the numerous interrelated deadlines.” *In re Syngenta*, 2016 WL 4705620, at *4. In any case, discovery is not the appropriate avenue to obtain the facts that form the basis of a complaint. *See e.g., Netto v. Amtrack*, 863 F.2d 1210, 1216 (5th Cir. 1989) (factual allegations precede discovery); *In re Medtronic, Inc. Sprint Fidelis Leads Prods. Liab. Litig.*, No. 08-1905, 2009 WL 294353, at

*2 (D. Minn. 2009) (“A plaintiff must adequately plead a claim before obtaining discovery, not the other way around.”).

Moreover, many of Plaintiffs’ new allegations are, on their face, based on information disclosed to Plaintiffs more than a year and up to nearly two years ago. *See, e.g.* Exhibit C, Plfs.’ Proposed Third Amended Master Complaint at ¶¶ 154, 234 (referring to testimony from company witness Dr. Amy Freedman, deposed on October 26, 2018, and Sanofi’s nurse tear sheet, produced on November 16, 2017); ¶¶ 235–41 (referring to Sanofi’s “Voices” Facebook page, information produced to Plaintiffs on December 15, 2017); ¶165 (allegations related to the French Health Inquiry and EMA label change, information produced to Plaintiffs on December 15, 2017). Plaintiffs’ claim that they have just learned “new” information is therefore incorrect. Rather, the only reasonable explanation for Plaintiffs’ motion at this stage of the litigation is an attempt to avoid future dismissals. Courts do not permit amendment under these circumstances. *Quinn for CryptoMetrics, Inc. v. Scantech Identification Beams Sys., LLC*, No. 5:13-cv-834, 2017 WL 2124487, at *2 (W.D. Tex. May 15, 2017) (“The Court finds, however, that the trustee is not seeking to merely correct an insufficiently stated claim—*i.e.*, that the adverse interest exception applies—but is instead trying to alter the facts previously pled in order to avoid dismissal. In such circumstances, leave to amend is not warranted.”); *In re Zofran (Ondansetron) Prod. Liab. Litig.*, No. 15-md-2657, 2018 WL 2291316, at *7 (D. Mass. May 18, 2018) (denying motion to amend where the court had already ruled on a motion to dismiss, explaining that courts are to “discourage any expectation that there will be leisurely repeated bites at the apple.”) (internal quotation marks and citations omitted). There is no legitimate reason for Plaintiffs’ amendments at this stage in the proceedings, and they should not be permitted.

CONCLUSION

Making Plaintiffs' alleged injury more nebulous does not save the thousands of claims filed years-and-years too late in this MDL. An amended complaint would not change this Court's dismissals of the *Johnson* and *Francis* cases or the many other cases similarly situated where Plaintiffs claim an injury six months after chemotherapy ended and thereafter never saw a healthcare provider or took other action, despite excitement of their attention to the knowledge or belief that their hair had not regrown normally. The amendment is instead unsupported—even by Plaintiffs' own experts—and certain to delay proceedings and consume resources in a re-do of the pleadings stage (along with discovery that would then follow) after years of litigation. For the reasons stated above, the Court should deny Plaintiffs' Motion.

Date: November 20, 2019

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on November 20, 2019, I electronically filed the foregoing with the Clerk of the Court using the ECF system which sent notification of such filing to all counsel of record.

/s/ Douglas J. Moore

EXHIBIT A

Filed Under Seal

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION	:	MDL NO. 2740
	:	SECTION "H" (5)
THIS DOCUMENT RELATES TO ALL CASES	:	HON. JANE TRICHE MILAZZO

**SECOND~~THIRD~~ AMENDED MASTER LONG FORM
COMPLAINT AND DEMAND FOR JURY TRIAL
(PARTIALLY REDACTED)**

1. COME NOW, Plaintiffs, through the Plaintiffs' Steering Committee, who submit this ~~Second~~Third Amended Master Long Form Complaint and Demand for Jury Trial ("~~Second~~Third Amended Master Complaint"). This ~~Second~~Third Amended Master Complaint sets forth common allegations of Plaintiffs who were injured as a result of their exposure to brand-name drug products Taxotere, Docefrez, Docetaxel Injection Concentrate, and Docetaxel Injection that were approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FDCA"). These brand-name drug sponsors, manufacturers, labelers, and distributors are Defendants Sanofi S.A., Aventis Pharma S.A., Sanofi US Services Inc., Sanofi- Aventis U.S. LLC, Sandoz Inc., Accord Healthcare, Inc., McKesson Corporation d/b/a McKesson Packaging ("McKesson"), Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc., Hospira, Inc., Sun Pharma Global FZE, Sun Pharmaceutical Industries, Inc. f/k/a Caraco Pharmaceutical Laboratories Ltd., Pfizer Inc., Actavis LLC f/k/a Actavis Inc., Actavis Pharma, Inc., and Sagent Pharmaceuticals, Inc. (collectively "Defendants") for damages and such other relief deemed just and proper.

2. This ~~Second~~Third Amended Master Complaint is intended to achieve efficiency and economy by presenting certain common allegations and common questions of fact and law that

generally pertain

to Plaintiffs adopting this Complaint. Plaintiffs plead all Counts of this ~~Second~~Third Amended Master Complaint and Jury Demand in the broadest sense, pursuant to all applicable laws and pursuant to choice of law principles, including the law of the each Plaintiff's home state.

3. This ~~Second~~Third Amended Master Complaint does not necessarily include all claims asserted in all ~~of~~ the transferred actions to this Court. It is anticipated that individual Plaintiffs will adopt this ~~Second~~Third Amended Master Complaint and selected causes of action herein through the use of a separate Short Form Complaint. Any individual facts, jurisdictional allegations, additional legal claims and/or requests for relief of individual Plaintiffs may be set forth as necessary in the Short Form Complaint filed by the respective Plaintiffs. This ~~Second~~Third Amended Master Complaint does not constitute a waiver or dismissal of any claims asserted in those individual actions, and no Plaintiff relinquishes the right to amend his or her individual claims to include additional claims as discovery and trials proceed.

INTRODUCTION

4. Taxotere is a chemotherapy drug administered to many who suffer primarily from breast cancer. Brand-name drug sponsors, manufacturers, labelers, and distributors of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, have known for years that these drugs cause permanent hair loss by preventing the regrowth of hair, a now well-documented side effect that for years has been publicized in numerous scientific studies, articles, and presentations. Despite this, these brand- name entities failed to warn patients and healthcare providers of the risk of permanent hair loss and report this risk to the Food and Drug Administration ("FDA"). Instead, Defendants hid this devastating ~~side effect. In fact, some brand-name entities still fail to disclose that permanent hair loss is a common~~ side effect.

5. Plaintiffs are women who were diagnosed with breast cancer, underwent

chemotherapy using Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and/or Docefrez, and now suffer from permanent hair loss, a side effect for which they were not warned and

were wholly unprepared. Had Plaintiffs and Plaintiffs' healthcare providers known that permanent hair loss could result, they would have selected a different treatment option—effective alternatives to these drugs that do not lead to this devastating side effect are used regularly.

6. As a result of this undisclosed side effect, Plaintiffs have struggled to return to normalcy, even after surviving cancer because an integral element of their identities, their hair, never returned. Plaintiffs are stigmatized with the universal cancer signifier—baldness—long after they underwent cancer treatment, and their hair loss acts as a permanent reminder that they are cancer victims. This permanent change has altered Plaintiffs' self-image, negatively impacted their relationships, and others' perceptions of them, leading to social isolation and depression even long after fighting cancer.

7. Defendants failed, and some still fail, to adequately warn that permanent or irreversible hair loss is a common side effect of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, and Plaintiffs have been unable to weigh this devastating possibility when deciding among treatment options. Plaintiffs seek recovery for their mental and physical suffering stemming from permanent or irreversible hair loss.

THE PARTIES

A. Plaintiffs

8. This ~~Second~~Third Amended Master Complaint is filed on behalf of all Individual Injured Plaintiffs ("Plaintiffs") whose claims are subsumed within MDL No. 2740. Plaintiffs in these individual actions have suffered personal injuries as a result of the use of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez. In addition, and where applicable, this ~~Second~~Third Amended Master Complaint is also filed on behalf of Plaintiffs' spouses, children,

parents, decedents, wards and/or heirs, all represented by Plaintiffs' counsel.

9. Plaintiffs have suffered personal injuries as a direct and proximate result of Defendants' conduct and misconduct as described herein and in connection with the design, development, manufacture, testing, packaging, promotion, advertising, marketing, distribution, labeling, warning, and sale of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez.

10. ~~Plaintiffs file these lawsuits within the applicable statute of limitations period of first suspecting that these drugs caused the appreciable harm they sustained.~~ Plaintiffs could not, by the exercise of reasonable diligence, have discovered ~~the wrongful cause of their injuries as the cause was unknown to Plaintiffs.~~ that their usage of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez resulted in their injuries. In fact, Defendants have yet to acknowledge that these drugs permanently prevent hair regrowth, and Plaintiffs did not suspect, nor did they have reason to suspect that ~~they had been injured, the cause of their injuries,~~ these drugs prevented hair regrowth or the tortious nature of the conduct causing their injuries until a date prior to the filing of these actions, which is less than the applicable limitations period for filing suit.

11. Additionally, Plaintiffs were prevented from discovering this information at an earlier date because: (1) Defendants misrepresented to the public, ~~the FDA,~~ and the medical profession that Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, are free from permanent side effects; (2) Defendants failed to disclose to the public, ~~the FDA,~~ and the medical profession their knowledge of the risk ~~of permanent side effects~~ that these drugs could permanently prevent hair regrowth; and (3) Defendants fraudulently concealed facts and information that could have led Plaintiffs to discover the liability of the Defendants.

B. Sanofi-Related ~~Entitites~~Entities

12. Defendant Sanofi S.A. f/k/a Sanofi Aventis S.A. is the owner and operator of a

multinational vertically integrated pharmaceutical company organized and existing under the laws of France with a principal place of business at 54 Rue La Boétie, 75008 Paris, France. Sanofi S.A. formed in 2004 after Sanofi-Synthelabo acquired Aventis Group, including subsidiary Defendant Aventis Pharma, S.A. Sanofi S.A. is engaged in research and development, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing of prescription drugs, including Taxotere. American Depositary Receipts for Sanofi SA are traded on the New York Stock Exchange.

It is the only publicly traded company among the various Sanofi entities named as defendants in the case.

13. Defendant Aventis Pharma S.A. is a corporation organized and existing under the laws of France with a principal place of business at 20 Avenue Raymond Aron, 92160 Antony, France. Aventis Pharma S.A. is a wholly owned subsidiary of Defendant Sanofi S.A. Defendant Aventis Pharma S.A. is the owner/holder of the patents for Taxotere. Aventis Pharma S.A. previously sought to protect Taxotere patents by filing an action for patent infringement in the United States District Court for the District of Delaware and availing itself of United States law.

14. Upon information and belief, at the direction of Sanofi S.A., Defendant Aventis Pharma S.A. licensed the patents for Taxotere to Defendants Sanofi US Services Inc. and Sanofi-Aventis U.S. LLC.

15. Defendant Sanofi US Services Inc. f/k/a Sanofi-Aventis U.S. Inc. is a Delaware corporation, with a principal place of business at 55 Corporate Drive, Bridgewater, New Jersey 08807. Sanofi US Services Inc. is a wholly owned subsidiary of Defendant Sanofi S.A. Defendant Sanofi US Services Inc. engages in research and development, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing of prescription drugs, including Taxotere.

16. Defendant Sanofi-Aventis U.S. LLC is a Delaware limited liability company, with a principal place of business at 55 Corporate Drive, Bridgewater, New Jersey 08807. Sanofi-Aventis U.S. LLC is a wholly owned subsidiary of Defendant Sanofi S.A., and Sanofi S.A. is Sanofi-Aventis U.S., LLC's sole member. Defendant Sanofi-Aventis U.S. LLC engages in research and development, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing of prescription drugs, including Taxotere.

17. Defendant Sanofi-Aventis U.S. LLC d/b/a Winthrop U.S. operates, promotes, markets, sells, distributes generic pharmaceutical products under the name of Winthrop U.S., which is a business unit and/or division operating within and part of Sanofi-Aventis U.S. LLC.

18. Since 2006, Defendants Sanofi-Aventis U.S. LLC and Sanofi US Services Inc. have collectively served as the U.S. operational front for Defendant Sanofi S.A. in the U.S. prescription drug market. Prior to 2006, Aventis Pharmaceuticals Inc. served as the U.S. operational front for Defendant Sanofi S.A. in the U.S. prescription drug market until Aventis Pharmaceuticals Inc. merged with Sanofi S.A.

19. Defendant Sanofi S.A. is the alter ego of wholly owned subsidiary Defendants Aventis Pharma S.A., Sanofi US Services Inc., and Sanofi-Aventis U.S. LLC; Defendant Sanofi S.A. is using these named subsidiary Defendants as its agents; and/or Defendant Sanofi S.A. and the named subsidiary Defendants are one single integrated enterprise.

20. Defendant Sanofi S.A.'s Executive Vice-President of Pharmaceutical Operations in 2004, Hanspeter Spek, publicly stated in Sanofi S.A.'s Annual Report that the company was committed to growing its international presence by focusing on the United States, noting that "no pharmaceutical firm can call itself international unless it has achieved success and made its mark [in the United States]."

21. According to Mr. Spek, Defendant Sanofi S.A. was well-suited to handle the

complexities of the U.S. pharmaceutical market, explaining:

When you look at current trends in the U.S., you see a form of regionalization between different states beginning to emerge. That's a sign that the U.S. market is also becoming more complex in response to the country's economic constraints, pressure on prices, and so on. These are factors that we know and are used to dealing with; we have the experience and the knowhow to cope with them in all serenity.

22. In fact, Defendant Sanofi S.A. has provided the financial resources and human capital, installing “a management team made up of a perfect mix of U.S. and European talents” and controlling the operations of subsidiary Defendants Aventis Pharma S.A., Sanofi-Aventis U.S. LLC and Sanofi US Services Inc. by providing financing, Sanofi S.A.’s unique manufacturing “know-how,” direction

of sales force, and management of operational risks to subsidiary Defendants Aventis Pharma S.A., Sanofi-Aventis U.S. LLC and Sanofi US Services Inc.

23. Defendant Sanofi S.A. represents itself as a global company with over 110,000 employees in more than 100 countries, including approximately 17,000 employees in the United States. Sanofi S.A. touts a global sales force of tens of thousands of representatives, noting that these sales representatives, including those in the United States, “embody the [Sanofi] Group’s values on a day-to-day basis.”

24. In addition, Defendant Sanofi S.A. manages the cash surpluses of subsidiary Defendants Aventis Pharma S.A., Sanofi-Aventis U.S. LLC and Sanofi US Services Inc., including controlling and transferring equity holdings among Sanofi S.A.’s subsidiaries. Sanofi S.A. includes the earnings of its subsidiaries in its annual reports, noting that 36.2% of its annual sales come from the United States.

25. Sanofi S.A. also represents that it has 17 manufacturing sites, 2 development centers, and 8 distribution hubs in the United States, located in Florida, Georgia, Maryland, Massachusetts, Missouri, Nevada, New Jersey, Pennsylvania, Puerto Rico, Tennessee, Washington, and Washington, D.C.

26. Furthermore, Defendant Sanofi S.A. formulates and coordinates the global strategy for Sanofi business and maintains central corporate policies regarding Sanofi subsidiaries, including subsidiary Defendants named herein, under the general guidance of the Sanofi group control. For example, Sanofi S.A. has a corporate tax policy overseen by Sanofi S.A.’s Tax Department.

27. Employees of Sanofi S.A. and its subsidiaries maintain reporting relationships that are not defined by legal, corporate relationships, but in fact cross corporate lines. For example, the ~~U.S.~~ U.S. heads of Human Resources, Communications, and Public Affairs are not affiliated with any specific

U.S. subsidiary but serve as heads of Sanofi’s North American organizations, overseeing strategies

and activities for the entire North American region. For Human Resources specifically, Defendant Sanofi S.A. has adopted the “One Sanofi, One HR” concept to harmonize and align human resources practices across of Sanofi S.A.’s business activities, blurring corporate lines. In 2013, Sanofi S.A. launched the Short Term Work Assignment Program (“SWAP”), an employee exchange program that features six-month job exchanges between Sanofi employees in mature and emerging markets.

28. Defendant Sanofi S.A. has a number of policies for employee benefits and salaries that cross corporate lines. In 2001, Sanofi launched the “essential protection” project. This project provided all employees, across corporate lines, with coverage against unexpected events: illness, death benefit, and short and long term disability. This project also provided for compulsory pensions for all employees. Sanofi S.A. also has a compensation policy that all Sanofi subsidiaries have to follow. This policy aims to offer all employees in all subsidiaries compensation that is superior to the average salary for the pharmaceutical market. Each subsidiary’s employee benefits and salary program is subject to a preliminary approval procedure by Sanofi S.A. This means that Sanofi S.A. dictates the salary levels and benefits that must be paid to employees of its subsidiaries. Defendant Sanofi S.A. also controls research and development activities for Defendants Sanofi- Aventis U.S. LLC and Sanofi US Services Inc. by defining priorities, coordinating work, and obtaining the industrial property rights under Sanofi S.A.’s name and at Sanofi S.A.’s own expense. As mentioned above, Sanofi has a global Research & Development organization that works closely with Sanofi’s Senior Leadership Team.

29. On November 6, 2015, Sanofi S.A. CEO Oliver Brandicourt presented a “strategic roadmap,” a plan to restructure the company and simplify the organizational structure. Before the restructuring, Research & Development, Industrial Affairs, Finance, Human Resources, Business Development & Strategy, External Affairs, Information Systems, Medical, Legal, Compliance, & Procurement were globalized functions. After the restructuring, Sanofi S.A. introduced plans to move

further to a Global Business Unit organization and divide its products into five globalized units: [8](#)

Diabetes and Cardiovascular, General Medicines and Emerging Markets, Specialty Care, Vaccines, and Animal Health. The restructuring additionally included plans to reshape Sanofi's global network of manufacturing plants. As a result of the restructuring Sanofi S.A. announced it would be cutting about 20 percent of its U.S. staff from its diabetes and cardiovascular unit alone with more U.S. staff cuts likely to come in the future.

30. Defendants Sanofi S.A. and Aventis Pharma S.A., through Sanofi-Aventis U.S. LLC and Sanofi US Services Inc., marketed Taxotere throughout the United States by providing marketing information regarding Taxotere to health care providers and similarly soliciting purchases for the drug.

31. Defendants Sanofi S.A. and Aventis Pharma S.A. expected that Taxotere would be sold, purchased, and used throughout the United States. In fact, Defendants Sanofi S.A. and Aventis Pharma S.A., through Sanofi-Aventis U.S. LLC and Sanofi US Services Inc., distributed and sold Taxotere to healthcare providers and patients throughout the United States.

C. Other Brand Name Drug Sponsors, Manufacturers, Labelers, and Distributors

32. In addition to the Sanofi-related entities, other brand-name entities obtained approval to market new drugs with the proprietary names Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate. Their new drug applications were approved under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), codified at 21 U.S.C. § 355(b)(2).

33. A 505(b)(2) application is a subset of NDA, and it is subject to the NDA approval requirements set out in section 505(b) and (c) of the FDCA. As such, it must satisfy the requirements for safety and effectiveness information.

34. A 505(b)(2) application contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference.

35. Accordingly, a 505(b)(2) applicant may rely on the findings of safety and effectiveness of a listed drug to the extent the new product seeking approval and the listed drug are the same. Otherwise, to the extent the products are different, a 505(b)(2) application, like a 505(b)(1) application, must include sufficient data to demonstrate that the product with those different aspects meets the statutory approval standard for safety and effectiveness.

36. A drug approved under the 505(b)(2) approval pathway is not a generic copy of a brand-name drug. Section 505(b)(2) is not an appropriate approval pathway for an application for a duplicate drug eligible for approval under section 505(j) of the FDCA (the Abbreviated New Drug Application process).

1. Sandoz

37. Defendant Sandoz Inc. (“Sandoz”) is a pharmaceutical company organized and existing under the laws of the State of Colorado with a principal place of business at 100 College Road West, Princeton, New Jersey 08540.

38. Defendant Sandoz has transacted and conducted business throughout the United States.

39. Defendant Sandoz has derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

40. At all relevant times, Defendant Sandoz has been in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docetaxel Injection approved by the FDA under New Drug Application (“NDA”) #201525.

41. The proprietary name for Defendant Sandoz’s branded drug is Docetaxel Injection.

42. Defendant Sandoz expected that Docetaxel Injection would be sold, purchased, and used throughout the United States.

43. Defendant Sandoz filed NDA application #201525 on September 16, 2010, under Section 505(b)(2). Its application relied for its approval on FDA's findings of safety and effectiveness

for the reference listed drug Taxotere.

44. Sandoz's formulation of Docetaxel Injection, however, is different from Taxotere in that it contains less polysorbate 80 and more 96 percent ethanol. Also, it contains polyethylene glycol 300 as a solubizer and anhydrous citric acid for pH adjustment.

45. Sandoz received FDA approval for NDA #201525 on June 29, 2011 and began marketing the drug in the United States on August 15, 2011.

46. When the drug was approved, a portion of the Patient Counseling Information read as follows: "Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration." It also stated that one of the "most common side effects of Docetaxel Injection" is "hair loss." Neither of these statements refer to permanent hair loss.

47. Since approval, Sandoz has submitted multiple Changes Being Effectuated Supplemental New Drug Applications ("CBE sNDA") to update labeling. It submitted a CBE sNDA (S-002) on July 29, 2011 that was approved on March 15, 2012, and a CBE sNDA (S-003) on August 15, 2013 that was approved on April 23, 2014. Neither submission, however, updated labeling concerning hair loss.

48. On October 21, 2016, the FDA approved Sandoz's CBE sNDA, submitted on March 7, 2016, "to include information on permanent or irreversible alopecia to Section 6.2 (Post-marketing Experience), Section 17 (Patient Counseling Information) of the Package Insert, and the Patient Package Insert (PPI) labeling."

49. As of December 2015, under "Post-Marketing Experiences," the labeling states: "Cases of permanent alopecia have been reported." Its Patient Counseling Information states that

“side effects such as [...] hair loss (cases of permanent hair loss have been reported) are associated with docetaxel administration.” Its patient information also states that the “most common side effects” include “hair loss, in most cases normal hair growth should return. In some cases (frequency not

known) permanent hair loss has been observed.”

50. There is no mention of the risk of permanent or irreversible hair loss, however, in the Warnings and Precautions or Adverse Reactions portions of its labeling.

2. *Accord Healthcare & McKesson*

51. Defendant Accord Healthcare, Inc. (“Accord”) is a pharmaceutical company organized and existing under the laws of the State of North Carolina with a principal place of business at 1009 Slater Road, Suite 210-B, Durham, North Carolina 27703.

52. Defendant McKesson Corporation d/b/a McKesson Packaging (“McKesson”) is a pharmaceutical company organized and existing under the laws of the State of Delaware with a principal place of business at One Post Street, San Francisco, California 94104.

53. Defendants Accord and McKesson have transacted and conducted business throughout the United States.

54. Defendants Accord and McKesson have derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

55. At all relevant times, Defendant Accord has been in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docetaxel Injection approved by the FDA under NDA #201195. Defendant Accord expected that Docetaxel Injection would be sold, purchased, and used throughout the United States.

56. At all relevant times, Defendant McKesson has been in the business of packaging and

distributing Docetaxel Injection approved by the FDA under NDA #201195. Defendant McKesson expected that Docetaxel Injection would be sold, purchased, and used throughout the United States.

57. Defendant Accord filed NDA #201195 on December 7, 2010, under Section 505(b)(2). Its application relied for its approval on FDA's findings of safety and effectiveness for the reference listed drug Taxotere.

58. Accord's two-vial formulation, however, was different from Taxotere's two-vial formulation in that it added new excipients citric acid (as a pH adjusting agent) and polyethylene glycol (PEG 400) (added to the diluent vial at 13 percent w/v). A one-vial formulation by Accord was later added in the same concentration and doses as the one-vial Taxotere, with the addition of a 160 mg / 8 mL "multiple dose" form.

59. Accord received FDA approval for NDA #201195 on June 8, 2011 and began marketing the drug in the United States on August 15, 2011.

60. When the drug was approved, a portion of the Patient Counseling Information read as follows: "Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration." It also stated that one of the "most common side effects of Docetaxel Injection" is "hair loss." Neither statement refers to permanent hair loss.

61. On November 14, 2013, Accord submitted a CBE sNDA (S-006) that was unrelated to hair loss. It was approved on July 3, 2014. Prior to that, Accord had also submitted a Manufacturing sNDA (S-004) that, upon information and belief, resulted in various labeling changes on or before April 5, 2013, which did not relate to hair loss.

62. Accord submitted a CBE sNDA (S-009) that was approved on July 26, 2016. As a result, the current label states that "[c]ases of permanent alopecia have been reported." Patient Counseling Information directs: "Explain to patients that side effects such as [...] hair loss (cases of permanent hair loss have been reported) are associated with docetaxel administration." The Patient

Information section now reads, in part: “The most common side effects of Docetaxel Injection include [...] hair loss, in most cases normal hair growth should return. In some cases (frequency not known), permanent hair loss has been observed.”

63. There is no mention of the risk of permanent or irreversible hair loss, however, in the Warnings and Precautions or Adverse Reactions portions of its labeling.

3. ~~4.~~ *Hospira Entities*

64. Defendant Hospira, Inc. is a pharmaceutical company organized and existing under the laws of the State of Delaware with a principal place of business at 275 N. Field Drive, Lake Forest, Illinois 60045.

65. Defendant Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc. is a pharmaceutical company organized and existing under the laws of the State of Delaware with a principal place of business at 275 N. Field Drive, Lake Forest, Illinois 60045.

66. Defendants Hospira, Inc. and Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc. (collectively “Hospira”) have transacted and conducted business throughout the United States.

67. Hospira has derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

68. At all relevant times, Hospira has been in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docetaxel Injection approved by the FDA under NDA #022234. Hospira expected that Docetaxel Injection would be sold, purchased, and used throughout the United States.

69. Hospira filed NDA #022234 on July 11, 2007 under Section 505(b)(2). Its application relied for its approval on FDA’s findings of safety and effectiveness for the reference listed drug Taxotere.

70. Hospira’s formulation, however, is different from Taxotere’s formulation in several

ways. First, upon the filing of its NDA in 2007, its pre-mixed, one-vial solution differed from Taxotere's original two-vial formulation, which required initial dilution. (Taxotere's one-vial, "ready- to-use" formulation was not FDA approved until 2010.) Second, it is packaged at a concentration of 10 mg / mL, which is one-fourth of the strength of two-vial Taxotere and one- half the strength of

one-vial Taxotere. Third, Hospira's 10 mg / mL formulation was marketed in a 160 mg vial, in addition to 20 mg and 80 mg vials. Fourth, whereas Taxotere labels all its dosage forms as "single-use," Hospira's 80 mg and 160 mg formulations are marketed as "multi-use." Fifth, unlike Taxotere, Hospira's Docetaxel Injection contains both citric acid and polyethylene glycol 300.

71. Hospira received FDA approval for NDA #022234 on March 8, 2011 and began marketing the drug in the United States on March 17, 2011.

72. When the drug was approved, a portion of the Patient Counseling Information read as follows: "Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration." It also stated that one of the "most common side effects of Docetaxel Injection" is "hair loss." Neither of these statements refer to permanent hair loss.

73. On September 11, 2013, Hospira submitted a "Prior Approval" sNDA (S-003) adding certain indications consistent with Taxotere's package insert at the time. Hospira also included in this sNDA new safety information concerning ethanol intoxication, which the FDA had requested Hospira add by letter of April 21, 2014. The FDA approved this sNDA on July 10, 2014. This update, the most recent revision, did not concern hair loss.

74. There is no mention of the risk of permanent or irreversible hair loss in its labeling.

4. ~~5.~~ *Sun Pharma Entities*

75. Defendant Sun Pharma Global FZE ("Sun Pharma Global") is a pharmaceutical company organized and existing under the laws of the Emirate of Sharjah with a principal place of business at Executive Suite #43, Block &, SAIF Zone, P.O. Box 122304, Sharjah, United Arab Emirates.

76. Defendant Sun Pharmaceutical Industries, Inc. f/k/a Caraco Pharmaceutical Laboratories, Ltd. (“Sun Pharma”) is a pharmaceutical company organized and existing under the laws of New Jersey with a principal mailing address of 270 Prospect Plains Road Cranbury, NJ 08512

United States.

77. Defendants Sun Pharma Global has transacted and conducted business throughout the United States, on its own behalf and through its agent and distributor Defendant Sun Pharma

78. Defendants Sun Pharma Global and Sun Pharma have derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

79. At all relevant times, Defendants Sun Pharma Global and Sun Pharma have been in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docefrez, approved by the FDA under NDA #022534. Defendants Sun Pharma Global and Sun Pharma expected that Docefrez would be sold, purchased, and used throughout the United States.

80. Defendant Sun Pharma Global filed NDA #022534 on April 23, 2009 under Section 505(b)(2). Its application relied for its approval on FDA’s findings of safety and effectiveness for the reference listed drug Taxotere.

81. Sun Pharma Global’s two-vial docetaxel formulation, however, is different from Taxotere’s two-vial formulation for several reasons. First, as opposed to Taxotere’s active ingredient vial, which solution is viscous, Sun Pharma Global’s active ingredient vial contains a powder. Second, and relatedly, Sun Pharma Global’s polysorbate 80 is found in the diluent vial. Third, Sun Pharma Global’s diluent vial contains a higher percentage of ethanol (35.4 percent) than Taxotere’s (13 percent). Fourth, Sun Pharma Global’s concentration is two times that of the two-vial Taxotere.

82. Sun Pharma Global received FDA approval for NDA #022534 on May 3, 2011 and began marketing the drug in the United States in May 2011.

83. When the drug was approved, a portion of the Patient Counseling Information read as follows: “Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration.” It also stated that one of the “most common side effects of” the drug is “hair loss.” Neither of these statements refer to permanent hair loss.

84. Sun Pharma Global submitted, through its agent Sun Pharma, a CBE sNDA (S-002) to the FDA on July 28, 2011, for a label change that was approved on July 13, 2012. It also submitted a “Prior Approval” sNDA (S-004) for a label change through its agent Sun Pharma on May 22, 2014, which was approved on October 30, 2014. Neither change related to hair loss.

85. Sun Pharma Global and Sun Pharma ceased marketing Docefrez in November 2015, and at no time has the labeling for Docefrez referred to permanent or irreversible hair loss.

5. ~~6.~~ *Pfizer*

86. Defendant Pfizer Inc. (“Pfizer”) is a pharmaceutical company organized and existing under the laws of the State of Delaware with a principal place of business at 235 E 42nd Street, New York, NY 10017.

87. Defendant Pfizer has transacted and conducted business throughout the United States.

88. Defendant Pfizer has derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

89. At all relevant times, Pfizer has been in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docetaxel Injection approved by the FDA under NDA #202356. Pfizer expected that its Docetaxel Injection would be sold, purchased, and used throughout the United States.

90. Pfizer filed NDA #202356 on September 13, 2013, under Section 505(b)(2). Its application relied for its approval on FDA’s findings of safety and effectiveness for the reference

listed drug Taxotere.

91. Pfizer's one-vial formulation, however, was different from Taxotere's one-vial formulation in that it added 130 mg / 13 mL and 200 mg / 20 mL dosage forms. Further, ethanol and propylene glycol were added as excipients in amounts greater than in Taxotere.

92. Pfizer received FDA approval for NDA #202356 on March 13, 2014 and began marketing the drug in the United States on June 23, 2014.

93. When the drug was approved, a portion of the Patient Counseling Information read as follows: "Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration." It also stated that one of the "most common side effects of" the drug is "hair loss." Neither of these statements refer to permanent hair loss.

94. Pfizer stopped marketing the 200 mg / 20 mL dosing of its Docetaxel Injection on October 31, 2016. In addition, Pfizer stopped marketing the 20 mg / 2 mL dosing and the 80 mg / 8 L dosing of its Docetaxel Injection on December 31, 2016.

95. Upon information and belief, Pfizer continues to market that 130 mg / 13 mL dosing of its Docetaxel Injection.

96. There is no mention of the risk of permanent or irreversible hair loss in its labeling.

6. ~~7.~~ *Actavis Entities*

97. Defendant Actavis Inc., now known as Actavis LLC, is a pharmaceutical limited liability company organized and existing under the laws of the State of Delaware with a principal place of business at 60 Columbia Road, Building B, Morristown, New Jersey 07960 and 400 Interpace Parkway, Parsippany, New Jersey 07054.

98. Defendant Actavis Pharma Inc. is a pharmaceutical company organized and existing under the laws of the State of Delaware with a principal place of business at 400 Interpace Parkway, Parsippany, New Jersey 07054. In 2016, Teva Pharmaceutical Industries, Ltd. acquired Defendant Actavis Pharma Inc. Prior to 2016, Actavis Pharma Inc. was a wholly owned subsidiary of

Defendant Actavis LLC f/k/a Actavis Inc.

99. Defendant Sagent Pharmaceuticals, Inc. (“Sagent”) is incorporated under the laws of Delaware and maintains a principal place of business at 1901 N. Roselle Road, Ste. 700, Schaumburg, IL 60195.

100. Defendants Actavis LLC f/k/a Actavis Inc. and Actavis Pharma Inc. (collectively “Actavis”) and Sagent transacted and conducted business throughout the United States.

101. Actavis and Sagent derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

102. At all relevant times, Actavis and Sagent was in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docetaxel Injection Concentrate approved by the FDA under NDA #203551. Actavis and Sagent expected that Docetaxel Injection Concentrate would be sold, purchased, and used throughout the United States.

103. Actavis filed NDA #203551 on March 14, 2012 under Section 505(b)(2). Its application relied for its approval on FDA’s findings of safety and effectiveness for the reference listed drug Taxotere.

104. Actavis and Sagent’s one-vial formulation, however, was different from Taxotere’s one-vial formulation because it is offered at an additional 140 mg dosage form, contains excipients citric acid and Kollidor 12 PF (Povidone k12), and uses reduced levels of polysorbate 80. After Actavis’ initial docetaxel approval, a 160 mg dosage form was also introduced.

105. Actavis received FDA approval for NDA #203551 on April 12, 2013 and began marketing these dosage forms on July 1, 2013.

106. When the drug was approved, a portion of the Patient Counseling Information read as follows: “Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration.” It also stated that one of the “most common side effects of” the drug is “hair loss.”

Neither of these statements refer to permanent hair loss.

107. Actavis submitted a CBE sNDA (S-001) on May 14, 2013, which was approved on November 4, 2013. Actavis also submitted a “Prior Approval” sNDA (S-002) on March 21, 2014,

which was approved on September 17, 2014. Neither resulting label change related to hair loss.

108. There is no mention of the risk of permanent or irreversible hair loss in its labeling.

JURISDICTION AND VENUE

109. Federal subject-matter jurisdiction in the constituent actions is based upon 28 [U.S.C.](#) ~~U.S.C.~~ § 1332(a). Plaintiffs allege the existence of subject-matter jurisdiction, and absent objection, there is complete diversity among Plaintiffs and Defendants and the amount in controversy exceeds \$75,000.

110. A substantial part of the events and omissions giving rise to Plaintiffs' causes of action occurred in the federal judicial district identified in the Short Form Complaint. Pursuant to 28 U.S.C.

§ 1391(a), venue is proper there.

111. Pursuant to the Transfer Orders of the Judicial Panel on Multidistrict Litigation, venue in actions sharing common questions with the initially transferred actions is proper in this district for coordinated pre-trial proceedings pursuant to 28 U.S.C. § 1407.

112. Defendants have significant contacts with the federal judicial district identified in the Short Form Complaint such that they are subject to the personal jurisdiction of the court in that district.

FACTUAL ALLEGATIONS

[A.](#) ~~Development, Approval, and Labeling Changes for Taxotere,~~ **Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez**

113. Taxotere is a drug used in the treatment of various forms of cancer, including breast cancer, and is a part of a family of cytotoxic drugs referred to as taxanes.

114. Taxanes are derived from yew trees, and unlike other cytotoxic drugs, taxanes inhibit the multiplication of cancer cells by over-stabilizing the structure of a cancer cell, which prevents the cell from breaking down and reorganizing for cell reproduction. They are widely used as chemotherapy agents.

115. The development of taxanes began in the 1960s. Bristol-Myers Squibb developed, manufactured, and distributed the first commercially available taxane in the United States, known as 20 Taxol (paclitaxel).

116. Taxol is the main competitor drug to Taxotere, and has been on the market since 1993.

117. Both docetaxel (Taxotere) and paclitaxel (Taxol) disrupt the microtubular network in cells that is essential for mitotic and interphase cellular function in the cell multiplication process.

118. Taxotere began as a two-vial product. One vial is called a concentrate, and it contains docetaxel, along with polysorbate 80 and residual amounts of ethanol. The other vial is a diluent, containing water and ethanol.

119. The concentrate vial and the diluent vial are combined to form a “premix.” A premix can be added to an intravenous bag to make a prefusion.

120. Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez are not purchased by patients at a pharmacy; rather, patients use of these drugs occurs via administration through injection and/or intravenously at a physician’s office or medical treatment facility.

121. In the 1980s scientists at Rhône-Poulenc Rorer S.A., Defendant Sanofi S.A.’s predecessor-in-interest, began developing Taxotere with the intention of making a more potent taxane. Since that time, Defendants Sanofi S.A., Aventis Pharma S.A., Sanofi US Services Inc., Sanofi- Aventis U.S. LLC, and their affiliates and predecessors-in-interest (collectively “Sanofi”) have controlled the development and been the owner, holder, or assignee of the patents related to Taxotere.

122. Phase I clinical testing of Taxotere began in 1990 (called the “TAX 001” study) and continued until 1992. Sanofi reported the results of clinical testing in May 1994.

123. Soon thereafter, on July 27, 1994, Sanofi applied for FDA approval for Taxotere under NDA #20449. The FDA’s Oncologic Drugs Advisory Committee panel unanimously denied approval of the drug, requesting more data on toxicity, side effects, and phase III test results.

124. After additional clinical testing, the FDA approved Taxotere in May 14, 1996 for

limited use—namely, for the treatment of patients with locally advanced or metastatic breast cancer

that had either (1) progressed during anthracycline-based therapy or (2) relapsed during anthracycline-based adjuvant therapy.

125. The label approved for Taxotere for this indication reflected the medical community's understanding that temporary hair loss is commonly associated with chemotherapy drugs and provided no information about the risk of permanent alopecia.

126. In fact, the clinical trial sponsored by Sanofi to support initial approval did not evaluate alopecia as a long-term side-effect of Taxotere.

127. ~~125.~~ After the initial approval, Sanofi sought and received FDA approval for additional indications. Based on self-sponsored clinical trials, Sanofi claimed Taxotere's superiority over competing chemotherapy products approved for breast cancer treatment, including claiming superior efficacy over the lower potency paclitaxel (Taxol), its primary competitor.

128. ~~126.~~ On June 22, 1998, the FDA approved a slightly broader indication for Taxotere that extended its use to patients with locally advanced or metastatic breast cancer as treatment after "failure of prior chemotherapy."

129. ~~127.~~ That same year, Sanofi obtained FDA approval in December 1999 for use of Taxotere in treating "locally advanced or metastatic non-small cell lung cancer after failure of prior platinum- based chemotherapy."

130. ~~128.~~ As with all prior FDA-approved indications for Taxotere, the drug was approved at this time, and until late 2002, only as a second-line of treatment, meaning that Sanofi was prohibited from promoting Taxotere for use in patients who had not undergone and failed a specified first-line of treatment.

~~129. As of December 23, 1999, hair loss was listed as a "possible side effect[]" of Taxotere." The label elaborated: "Loss of hair occurs in most patients taking Taxotere (including the hair on your head, underarm hair, pubic hair, eyebrows, and eyelashes) [...]. Once you have completed all~~

~~your treatments, hair generally grows back.”~~

131. ~~130.~~ Sanofi obtained FDA approval in November 2002 for use of Taxotere “in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.”

132. ~~131.~~ Sanofi obtained FDA approval in May 2004 for use of Taxotere “in combination with prednisone as a treatment for patients with androgen independent (hormone refractory) metastatic prostate cancer.”

133. ~~132.~~ Also that year, Sanofi obtained FDA approval in August 2004 for use of Taxotere “in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.”

134. ~~133.~~ In March 2006, Sanofi obtained FDA approval for use of Taxotere “in combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.”

135. ~~134.~~ Sanofi obtained FDA approval in October 2006 for use of Taxotere “in combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN).” In September 2007, FDA approved a broader SCCHN indication that removed the condition of inoperability.

~~135. The 2010 version of the prescribing information stated under “Patient Counseling Information” that “side effects such as [...] hair loss are associated with docetaxel administration.” “Patient Information” indicated that the “most common side effects of TAXOTERE include: [...] hair loss.” The document contains no mention of irreversible or permanent hair loss. The November 2014 version of this labeling information contains the same text.~~

136. Sanofi obtained FDA approval in May 2010 to add language related to pediatric safety and efficacy, including: “The overall safety profile of TAXOTERE in pediatric patients receiving monotherapy or TCF was consistent with the known safety profile for adults.” Additional changes to this label included a number of edits described by Sanofi as “housekeeping” that, among other things, deleted the phrase “hair generally grows back” and added “most common side effects of TAXOTERE include: [...] hair loss” to the “Patient Information” section of the label. As with previous labels, the May 2010 label provides no information about irreversible or permanent hair loss.

137. On March 5, 2015, Sanofi conducted an audit of its U.S. product labels, finding that the U.S. label for Taxotere did not include the required safety information, including information about persisting alopecia. Sanofi determined this information should have been added to the U.S. label in 2011.

138. Shortly thereafter, on March 23, 2015, FDA requested information from Sanofi regarding instances of permanent alopecia. On April 8, 2015, Sanofi issued its response to FDA, identifying that out of 2118 cases of reported alopecia from Taxotere patients, 89 (4.2%) appeared to be permanent.

139. In response, FDA requested on October 5, 2015 that Sanofi provide any additional information on permanent or irreversible alopecia and amend the Taxotere label to identify permanent alopecia in the “Adverse Reactions” section of the label.

140. ~~137.Sanofi~~ On November 11, 2015, Sanofi issued a Final Clinical Overview of Permanent Alopecia, finding a causal association between Taxotere and permanent alopecia. Sanofi then submitted a CBE sNDA on November 24, 2015 ~~concerning~~ “adding the language “cases of permanent ~~or irreversible~~ alopecia.”~~138.~~ On December 11, 2015, FDA approved the sNDA. Under have been reported” to the “Adverse Reactions” and “Patient Counseling Information,” sections of the ~~new label text reads: “Explain to patients that side effects such as [...] hair loss (cases of permanent hair loss have been reported) are associated with docetaxel administration.”~~ Additionally,

~~under “Patient Information” label. Sanofi also made changes to the “Patient Information” section of the label~~ ~~states~~ adding that the “most common side effects of TAXOTERE include: [...] “hair loss: in most cases normal hair growth should return. In some cases (frequency not known) permanent hair loss has been observed.” ~~This is the latest and currently operative warning regarding permanent or irreversible alopecia in the Taxotere label. The label contains no mention of irreversible or permanent hair loss under “Warnings and Precautions” or~~ The FDA approved Sanofi’s sNDA on December 11, 2015.

141. On April 11, 2018, Sanofi submitted a Prior Approval sNDA, request that the Taxotere label be updated to identify adverse events occurring at the conclusion of the follow-up period in TAX 316 in 2010. Among the adverse events identified by Sanofi included 29 patients who had alopecia ongoing at a median follow-up of 10-years. FDA approved Sanofi’s proposed label change on October 5, 2018.¹

~~“Adverse Reactions.”~~

B. ~~III.~~ **Defendants’ Duties Under the FDCA and State Law**

142. ~~139.~~ The primary responsibility for timely communicating complete, accurate and current

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/020449Orig1s079ltr.pdf safety and efficacy information related to prescription drugs rests with NDA holders/drug sponsors (such as manufacturers or labelers) and their assigns or agents; they have superior, and in many cases exclusive, access to the relevant safety and efficacy information, including post- market complaints and data.

143. ~~140.~~ To fulfill their essential responsibilities, these entities must vigilantly monitor all reasonably available information. They must closely evaluate the post-market clinical experience of their drugs and timely provide updated safety and efficacy information to the healthcare community and to consumers.

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144. ~~141.~~ When monitoring and reporting adverse events, as required by both federal regulations and state law, time is of the essence. The purpose of monitoring a product's post-market experience is to detect potential safety signals that could indicate to drug sponsors and the medical community that a public safety problem exists. If, for example, a manufacturer were to delay in reporting post-market information, that delay could mean that researchers, FDA, and the medical community are years behind in identifying a public safety issue associated with the drug. In the meantime, more patients are harmed by using the product without knowing, understanding, and accepting its true risks. This is why drug sponsors must not only completely and accurately monitor, investigate and report post-market experiences, but they must also report the data in a timely fashion.

145. ~~142.~~ Because complete information about the safety of a drug cannot be known at the time of approval, and because the true picture of a product's safety profile emerges over time because of use by patients, it is a central premise of federal drug regulation that the NDA holders and their assigns or agents—not the FDA—bear responsibility for the content of its label at all times. Consequently, NDA holders are primarily responsible for crafting an adequate label and ensuring that warnings remain adequate as long as the drug is on the market.

146. ~~143.~~ A drug is “misbranded” in violation of the FDCA when its labeling is false and misleading, or does not provide adequate directions for use and adequate warnings. See 21 U.S.C. §§ 321(n); 331(a), (b), (k); 352(a), (f). A drug's labeling satisfies federal requirements if it gives physicians and pharmacists sufficient information—including indications for use and “any relevant hazards, contraindications, side effects, and precautions”—to allow those professionals “to use the drug safely and for the purposes for which it is intended.” 21 C.F.R. § 201.100(c)(1).

147. ~~144.~~ As part of their responsibility to monitor post-market clinical experiences with the drug and provide updated safety and efficacy information to the healthcare community and to consumers, each approved NDA applicant, whether under 505(b)(1) or (2), “must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience,

post marketing clinical investigations, post marketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.” 21 C.F.R. § 314.80(b). Any report of a “serious and unexpected” drug experience, whether foreign or domestic, must be reported to the FDA within 15 days and must be promptly investigated by the manufacturer. 21 C.F.R. § 314.80(c)(1)(i-ii). Most other adverse event reports must be submitted quarterly for three years after the application is approved and annually thereafter. 21 C.F.R. § 314.80(c)(2)(i). These periodic reports must include a “history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).” 21 C.F.R. § 314.80(c)(2)(ii).

148. ~~145.~~ Federal law requires labeling to be updated as information accumulates: “labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.” 21 C.F.R. § 201.57(c)(6)(i). Thus, for example, drug manufacturers must warn of an adverse effect where there is “some basis to believe there is a causal relationship between the drug

and the occurrence of the adverse event.” 21 C.F.R. § 201.57(c)(7).

149. ~~146.~~ All changes to drug labeling require FDA assent. 21 C.F.R. § 314.70(b)(2)(v)(A). Brand-name drug sponsors, including those whose drugs were approved under Section 505(b)(2), may seek to change their approved labels by filing a supplemental application. 21 C.F.R. § 314.70.

150. ~~147.~~ One regulation, the “Changes Being Effected” (CBE) regulation, permits a manufacturer to unilaterally change a drug label to reflect “newly acquired information,” subject to later FDA review and approval. 21 C.F.R. § 314.70(c)(6)(iii). Newly acquired information includes “new analyses of previously submitted data.” 21 C.F.R. § 314.3(b). Thus, for instance, if a drug sponsor were to determine that a warning were insufficient based on a new analysis of previously existing data, it could submit a CBE and change its labeling.

151. ~~148.~~ The longer a drug sponsor delays updating its labeling so that it reflects current

safety information, the more likely it is that medical professionals will continue to prescribe drugs without advising patients of harmful side effects, and the more likely it is that patients will suffer harmful side effects without the opportunity to evaluate risks for themselves.

C. ~~III.~~ Defendants Knew ~~That~~~~that~~ Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate May Cause Permanent Alopecia.

152. In 1997, Sanofi initiated TAX 316, a self-sponsored clinical trial comparing the effects of a regimen of fluorouracil, doxorubicin, and cyclophosphamide (“FAC”) with a regimen of docetaxel, doxorubicin, and cyclophosphamide (“TAC”) in patients with operable node-positive breast cancer. A total of 1040 patients from 112 centers participated in TAX 316 with 744 patients receiving TAC and 736 receiving FAC. In 2004, an interim analysis of TAX 316’s 55-month median follow-up data demonstrated that 3.2% of patients who took Taxotere had persistent alopecia.

153. ~~149.~~ Beginning in 1998, Sanofi sponsored a trial entitled GEICAM 9805. It was initiated to compare the effects of a regimen of fluorouracil, doxorubicin, and cyclophosphamide (“FAC”) with a regimen of docetaxel, doxorubicin, and cyclophosphamide (“TAC”) in patients with high- risk,

node-negative breast cancer. Between June 1999 and March 2003, a total of 1060 patients from 55 centers were randomly assigned to receive either TAC or FAC. By 2005, it knew that the GEICAM 9805 study demonstrated that 9.2 percent of patients who took Taxotere had persistent alopecia, ~~or hair loss, for up to 10 years and 5 months, and in some cases longer.~~

154. In March 2006, Sanofi’s pharmacovigilance department received an inquiry from a physician about the reversibility of alopecia following Taxotere treatment, noting that a patient had been experiencing alopecia since 2004. In response, Sanofi’s Global Safety Officer for Taxotere internally acknowledged that cases of irreversible alopecia had occurred during Sanofi’s clinical trials for Taxotere and that the medical literature might contain additional reports of irreversible alopecia. Despite this, Sanofi’s Global Safety Officer advised against doing a literature search on the topic of irreversible alopecia and Taxotere. In addition, Sanofi withheld this information from the Taxotere label and concealed it from the medical community and consumers, including Plaintiffs.

155. ~~150.~~ In December 2006, an oncologist from Denver, Colorado, Dr. Scot Sedlacek, presented a study entitled “Persistent significant alopecia (PSA) from adjuvant docetaxel after doxorubicin/cyclophosphamide (AC) chemotherapy in women with breast cancer.” Dr. Sedlacek tracked patients in three groups: Group A (doxorubicin regimen without a taxane); Group B (doxorubicin plus paclitaxel) and Group C (doxorubicin plus docetaxel). No women in Group A or Group B experienced persistent significant alopecia, but 6.3 percent of those in Group C did. Dr. Sedlacek concluded “that when docetaxel is administered after 4 doses of AC, there is a small but significant possibility of poor hair regrowth lasting up to 7 years. Such an emotionally devastating long term toxicity from this combination must be taken into account when deciding on adjuvant chemotherapy programs in women who likely will be cured of their breast cancer.”

156. ~~151.~~ On November 21, 2008, Sanofi responded to an inquiry from a patient in the United Kingdom concerning Taxotere and the incidence of permanent alopecia. That letter acknowledged that “one reference of non-reversible alopecia” had been identified. Its letter cited a paper published

in the journal of Clinical Oncology for the proposition that “clinical studies ... showed one case of non-reversible alopecia at the end of the study.” The letter also cited another paper from the New England Journal of Medicine, which stated that “studies involving Taxotere in combination with doxorubicin and cyclophosphamide observed alopecia to be ongoing at the median follow-up time of 55 months in 3 percent of patients at the end of the chemotherapy.”

157. ~~152.~~ In 2009, the British Journal of Dermatology published an article entitled “Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer.” That article reported a case in which a 58-year-old woman “developed diffuse and irreversible alopecia 7-years ago, after being treated with six cycles of docetaxel ... every 3 weeks for a local occurrence.” She did not have alopecia before administration of the chemotherapy. The article concluded “the irreversibility can be attributed only to the cytotoxic effect of docetaxel.”

158. By early 2010, Sanofi had received reports from hundreds of women describing their permanent hair loss following treatment with Taxotere. Despite this fact, Sanofi withheld this

information from the label and concealed it from the medical community and consumers, including Plaintiffs.

159. ~~153.~~ On March 4,5, 2010, The Globe and Mail, a Canadian newspaper, published an article entitled “Women who took chemo drug say they weren’t warned of permanent hair loss.” The article explained: “Women who took a drug to fight breast cancer say they were never warned of a side effect—permanent hair loss—that left them looking sick long after they were treated for the disease.” The article described this permanent hair loss as a “lasting side effect of the chemotherapy drug Taxotere, in combination with other drugs.” The article included sufferers from Montreal, Canada; Brittany, France; and Oklahoma who had been treated with Taxotere. The article explained that the “side effect of persistent alopecia is suffered by about 3 percent of patients who take Taxotere with other chemotherapy drugs, according to the manufacturer’s own studies,” but that a “different study suggests that the incidence of persistent alopecia could be as high as 6 percent.”

160. ~~154.~~ The Globe and Mail article also cited medical oncologist Dr. Hugues Bourgeois of Le Mans, France, “who presented research on 82 patients with persistent alopecia at the San Antonio Breast Cancer symposium this winter.” Dr. Bourgeois described the choice he gives his patients— twelve cycles of Taxol or four cycles of Taxotere, where the risk of hair loss is higher. According to Dr. Bourgeois, most choose Taxol, which Dr. Bourgeois said “works just as well on breast cancer.”

161. ~~155.~~ On March 6, 2010, CBS News published an article entitled “Sanofi’s Latest Challenge: Women Who Say Its Chemotherapy Left Them Permanently Bald.” The article described a group of women who called themselves “Taxotears” and encouraged women who have lost all their hair to report the adverse events to Sanofi and drug watchdog authorities. It also noted that “Taxotere’s official prescribing information ... makes no mention of permanent alopecia,” and that “small studies suggest that as many as 6.3 percent of patients lose all their hair forever.”

162. ~~156.~~ The CBS News article also mentioned that the Medicines and Healthcare products Regulatory Agency in the United Kingdom noted that “it was aware of one study in which 22 of 687 patients (about 3 percent) had persistent baldness after nearly five years.”

163. ~~157.~~ On May 10, 2010, an article by Ben Tallon, MBChB, and others entitled “Permanent chemotherapy-induced alopecia: Case report and review of the literature” was published online. That article described “a case of permanent hair loss following standard dose chemotherapy with docetaxel, carboplatin, and trastuzumab for the treatment of breast carcinoma.” There, the “lack of evidence for alopecia with trastuzumab, and the exposure to only a single infusion of standard dose carboplatin, suggests that docetaxel is the implicated agent.” The article also explained: “Permanent [chemotherapy-induced alopecia] has been described following the use of ... docetaxel.”

164. Later in 2010, Sanofi completed its analysis of the ten-year follow-up results for TAX 316, the clinical trial used to support the adjuvant breast cancer indication. This analysis found that the number of women reporting persisting hair loss had increased from the 22 patients reported in 2004 to 29 patients out of the 687 patients tracked into follow-up. This represented an increase in the incidence of persistent alopecia from approximately 3% to 4.2%. Sanofi had previously decided in 2009 not to update the U.S. label with the follow-up data from TAX 316. Instead, Sanofi submitted to the FDA only the Final Clinical Study Report for TAX 316, which is over a thousand pages long, without submitting a labeling change. In addition, Sanofi continued to conceal this information from the medical community and consumers, including Plaintiffs.

165. In March of 2011, the French Health Authorities responded to Sanofi’s overview of persisting alopecia, concluding that patients and healthcare providers should be provided information about the risk of permanent alopecia given the serious psychological consequences of this adverse effect.

166. The following month, Sanofi’s Compliance Department issued an internal audit of drug labeling for various drug products, including Taxotere, to evaluate the accuracy and completeness of the safety data presented in the drug labeling. For Taxotere, the audit revealed that the labeling failed to include the incidence rate of persistent alopecia from TAX 316. Sanofi did not add this information to the label until 2018.

167. In June of 2011, the European Medicines Agency adopted the consensus of the French Health Authorities regarding persistent alopecia, informing Sanofi that the label for Taxotere needed to be updated to inform patients of the risk of irreversible alopecia. Sanofi updated the Taxotere label distributed in the European Union but did not update the label in the United States. Instead, Sanofi continued to conceal this information from the medical community and consumers in the United States, including Plaintiffs.

168. ~~158.~~Also in 2011, the American Journal of Dermatopathology published a study entitled “Permanent Alopecia After Systemic Chemotherapy: A Clinicopathological Study of 10 Cases,” by Mariya Miteva, MD and others. The article discussed “the histological features of 10 cases of permanent alopecia after systematic chemotherapy with taxanes (docetaxel),” including 6 cases in which the patients took docetaxel for breast cancer. “All patients had moderate to very severe hair thinning ~~...~~”

169. ~~159.~~ On May 9, 2012, the Annals of Oncology published an article entitled “Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/ cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients,” by Nicolas Kluger, M.D., Ph.D., among others. It reported that, since 2009, “nine cases of permanent scalp alopecia after systemic chemotherapy related to taxanes used to treat breast cancer have been reported ... Docetaxel was almost always involved, alone in seven cases ... or in association with carboplatin ... and trastuzumab.”

170. ~~160.~~ In October 2013, Drs. Nicola Thorp, Felicity Swift, Donna Arundell and Helen Wong presented at Clatterbridge Cancer Centre in the United Kingdom on “Long Term Hair Loss in Patients with Early Breast Cancer Receiving Docetaxel Chemotherapy.” Their study was based on a questionnaire sent in October 2013 to patients who received docetaxel in 2010. Out of 189 questionnaires, 134 were returned. “Of those responding 21 (15.8 percent) had significant persistent scalp hair loss.” The presentation concluded: “Long term significant scalp alopecia (hair lasting for up to 3.5 years following completion of chemotherapy) may affect 10-15 percent of patients following docetaxel for EBC. This appears to be unrelated to other patient and treatment

characteristics ... This risk should be discussed routinely (as part of the process of informed consent) with all patients embarking upon docetaxel as a component of management of EBC.”

171. ~~161.~~ This Clatterbridge study was also published at the 2014 San Antonio Breast Cancer Symposium.

172. ~~162.~~ On November 10, 2015, the Journal of Clinical Oncology published an article entitled

“Epirubicin Plus Cyclophosphamide Followed by Docetaxel Versus Epirubicin Plus Docetaxel Followed by Capecitabine As Adjuvant Therapy for Node-Positive Early Breast Cancer: Results From the GEICAM/2003-10 Study.” This article reviewed and reiterated the connection between docetaxel and long-term alopecia:

Patients who received [docetaxel] not only had to wear a wig for a longer period of time but also reported a significantly higher proportion of long-term incomplete scalp hair recovery and permanent wig use after therapy. This adverse effect, probably related to docetaxel ... has previously been described by others. Sedlacek reported that approximately 6% of patients who received adjuvant docetaxel for early BC had persistent alopecia, whereas this toxicity was not seen in 384 patients receiving nondocetaxel adjuvant regimens. Kluger et al reported 20 patients with BC with persistent hair loss of androgenetic-like pattern after adjuvant treatment with CEF followed by docetaxel. Consequently, a prospective study of the efficacy of scalp hypothermia in the prevention of docetaxel-induced persistent alopecia is ongoing at one of the centers participating in the present trial.

173. ~~163.~~ Despite this, hair loss was listed as a “possible side effect[] of Taxotere” that “generally grows back” in a Patient Information Letter circulated by Sanofi beginning in December 23, ~~1999.~~ 1999 and an informational brochure given to oncology nurses in 2006.

174. ~~164.~~ By contrast, the labeling for Taxotere approved by the European Medicines Agency in 2005 acknowledged that “[c]ases of persisting alopecia have been reported.” It also stated in a tabulated list of adverse reactions in breast cancer that took into account node-positive breast cancer (from ~~a study entitled~~ TAX 316) and node-negative breast cancer (from GEICAM 9805) that alopecia is a “[v]ery common adverse reaction,” with persisting alopecia occurring under three percent of the time.

175. Likewise, in a self-sponsored clinical trial, the informed consent form provided by Sanofi to Canadian patients disclosed irreversible alopecia as a possible side effect but a similar

informed consent form provided to United States patients in 2006 and 2007 did not. Again, Sanofi concealed this information from patients in the United States.

176. ~~165.~~ In the September 28, 2007 version of the Highlights of Prescribing Information in the

United States, alopecia is listed as one of the most common adverse reactions. There is no mention of permanent alopecia.

177. ~~166.~~ The April 2010 version of Taxotere's United States labeling ~~still~~ stated that "hair generally grows back." That language does not appear in the ~~2011~~ May 2010 version of Taxotere's label. Instead, the 2011 version of the prescribing information stated under "Patient Counseling Information" that "side effects such as ... hair loss are associated with docetaxel administration." "Patient Information" indicated that the "most common side effects of TAXOTERE include: ... hair loss." The document contains no mention of irreversible or permanent hair loss. Instead, it states that "alopecia" is one of the most common adverse reactions. The November 2014 version of this labeling information contains the same text.

178. ~~167.~~ In May 2015, Sanofi UK updated its Taxotere label. That version states that a "[v]ery common" side effect is "hair loss (in most cases normal hair growth should return)."

179. ~~168.~~ On June 12, 2015, Canada's Taxotere labeling changed. Its new labeling stated: "Hair loss may happen shortly after treatment has begun. Your hair should grow back once you've finished the treatment. However, some patients may experience persistent hair loss."

180. ~~169.~~ In August 2015, Australia's Taxotere labeling changed. Its new labeling stated that alopecia was "observed to be ongoing at the median follow-up time of 55 months."

181. ~~170.~~ In the United States, Sanofi submitted a CBE on November 24, 2015 concerning permanent alopecia.

182. ~~171.~~ On December 11, 2015, FDA approved the CBE. Under the "Adverse Reactions" and "Patient Counseling Information," ~~the new text reads: "Explain to patients that side effects such as ... hair loss ("~~ sections of the label, Sanofi added the language that "cases of permanent hair loss have been reported) ~~are associated with docetaxel administration." Additionally, under, "In the "Patient Information," the label states"~~ section, Sanofi added that the "most common side effects of TAXOTERE include: ... "hair loss: in most cases normal hair growth should return. In some cases (frequency not known) permanent hair loss has been observed."~~The label contains no mention of irreversible or permanent hair loss under "Warnings and Precautions" or "Adverse Reactions."~~

183. On April 11, 2018, Sanofi submitted a Prior Approval sNDA, request that the Taxotere label be updated to identify adverse events occurring at the conclusion of the follow-up period in TAX 34

316 in 2010. Among the adverse events identified by Sanofi included alopecia still ongoing at median follow-up of 8-years. FDA approved Sanofi's proposed label change on October 5, 2018.

184. ~~172.~~ Upon information and belief, Defendants failed to comply with the FDA postmarketing reporting requirements under 21 C.F.R. § 314.80 by, among other things, failing to report each adverse drug experience concerning the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate products, whether foreign or domestic, including Plaintiffs' injuries complained of herein, as soon as possible but in no case later than 15 calendar days after initial receipt of the information by Defendants, failing to promptly investigate all adverse drug experiences concerning these drug products that are the subject of these postmarketing 15-day Alert reports, failing to submit follow up reports within 15 calendar days of receipt of new information or as requested by the FDA, and, if additional information is not obtainable, failing to maintain records of the unsuccessful steps taken to seek additional information.

185. ~~173.~~ Also, consistent with the Changes Being Effected regulations, Defendants had and continue to have a duty to initiate a change to the products' labels to reflect the true levels of risk, including the risk of developing Plaintiffs' injuries complained of herein. To this day, Defendants have not adequately satisfied their duty to update the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate products' labeling or prescribing information to reflect their knowledge as to the true risks of developing the injuries complained of herein.

D. ~~IV.~~ Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate Caused Permanent Alopecia in Many Breast Cancer Patients.

186. ~~174.~~ Chemotherapy is known to cause temporary and reversible hair loss. Hair loss occurs because chemotherapy targets rapidly dividing cells (both normal, healthy cells as well as cancer cells) including hair follicles. Hair follicles, the structures in the skin filled with tiny blood

vessels that make hair, are some of the fastest growing cells in the body, thus, hair follicles are some of the most likely cells to be damaged by chemotherapy.

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187. ~~175.~~ There are 100,000 hair follicles on the scalp that typically grow about 0.3 to 0.4 mm a day or about six inches a year. For hair production, hair follicles undergo a cycle that consists of three phases: the anagen phase (growth), the catagen phase (transition), and the telogen phase (resting). During the anagen phase, the cells at the root of the hair follicle are dividing rapidly and an entire hair shaft from tip to root is formed. The matrix cells, which build the hair shaft, have a cell cycle length of approximately 18 hours. Approximately 90 percent of the hair on the scalp is normally in the anagen phase.

188. ~~176.~~ The catagen phase is a short transitional phase that occurs at the end of the anagen phase when growth of a hair stops. Only about 3 percent of hair follicles are in the catagen phase at any time.

189. ~~177.~~ The hair follicle is completely at rest during the telogen phase and, at the end of the telogen phase, the hair falls out and a new hair is supposed to start growing in the hair follicle beginning the hair cycle again with the anagen phase. Around 6 to 8 percent of all hair is regularly in the telogen phase.

190. ~~178.~~ Chemotherapy causes the matrix cells to stop dividing abruptly in the anagen phase.

As a result, the portion of the hair shaft that is the closest to the skull narrows and subsequently breaks within the hair canal. For this reason, hair loss usually begins one to three weeks after the initiation of chemotherapy and hair may fall out very quickly in clumps or gradually.

191. ~~179.~~ Because the majority of hair on the scalp is in the anagen phase during any given period, the hair loss that results from chemotherapy can be quite significant and visible.

192. ~~180.~~ The effects of chemotherapy on hair follicles results in temporary hair loss that lasts until the telogen phase is complete and a new hair cycle begins. According to the Mayo Clinic,

hair can be expected to grow back after chemotherapy within three to six months. Dr. Ralph M. Trueb, the author of several articles related hair loss associated with chemotherapy, also states that hair regrowth

following chemotherapy treatment will occur within three to six months after cessation of treatment.

193. ~~181.~~ Unlike the temporary and reversible alopecia that ordinarily results from chemotherapy, Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate cause Permanent Chemotherapy Induced Alopecia, ~~which is defined as an absence of or incomplete hair regrowth.~~

194. There is no single definition for Permanent Chemotherapy Induced Alopecia and the amount of time to establish permanent hair loss varies from patient to patient, including among Plaintiffs. The scientific literature has variously referred to Permanent Chemotherapy Induced Alopecia as occurring between twelve to twenty-four months following chemotherapy treatment. Some literature has indicated that hair loss can be deemed “persistent” six months beyond the completion of chemotherapy.

195. Sanofi has stated in court filings that “persistent” alopecia generally describes hair loss for some duration of time following chemotherapy (e.g., 3 days, 30 days, 3 months, 6 months, etc.) and carries with it the potential for hair regrowth to occur.

196. Sanofi has also stated in court filings that “irreversible” or “permanent” alopecia, at a basic level means that an individual’s hair will never regrow.

197. Before this litigation and after, Sanofi has described Permanent Chemotherapy Induced Alopecia in a number of different ways. Employees of Sanofi have testified that permanent hair loss does not necessarily mean hair loss of six months. In 2010, Sanofi’s Global Safety Officer concluded it was reasonable to assume that chemotherapy induced alopecia is “permanent” if alopecia persists for longer than four years following chemotherapy treatment. Consistent with that conclusion, in August of 2018, Sanofi’s Global Safety Officer stated that it is reasonable to consider alopecia to be permanent if hair has not regrown for four years after chemotherapy. Nevertheless, in 2015, Sanofi’s Global Safety Officer utilized a two-year cut off for deciding that chemotherapy

induced

alopecia is “permanent.” Internal email correspondence indicates that the company chose a two-year cut off in order to underreport to the FDA the incidence of permanent hair loss.

198. Upon information and belief, the varying definitions of Permanent Chemotherapy Induced Alopecia, as described above, were not reasonably knowable to prescribers or consumers of Taxotere, including Plaintiffs.

199. The Permanent Chemotherapy Induced Alopecia caused by Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate is not limited to the scalp and can affect hair follicles throughout the body.

200. ~~182.~~ Patients who receive Taxotere without any other type of chemotherapy have experienced permanent hair loss all over their bodies. For example, one oncologist reported he was unlikely to prescribe Taxotere in early stage breast cancer patients because of the toxicity of the drug. When prescribing Taxotere in early stage breast cancer cases, he recommended lower dosage levels over a longer period of time. His patients who have received Taxotere have experienced permanent hair loss.

201. ~~183.~~ Also, the GEICAM 9805, a study sponsored by Sanofi produced evidence that over 9 percent of high risk breast cancer patients who were administered Taxotere suffered permanent alopecia with hair loss lasting, in some cases, over ten years.

202. ~~184.~~ Dr. Sedlacek’s 2006 study, as described above, further demonstrates that Taxotere causes permanent hair loss. His study divided patients he treated from January of 1994 to December of 2004 into three groups. The first group, which contained 258 patients, received Doxorubicin. None suffered permanent alopecia. The second group, which contained 126 patients, received Doxorubicin and Taxol. Again, none suffered permanent alopecia. The third group contained 112 patients who received Doxorubicin and Taxotere. Of those patients, 6.3 percent

suffered permanent alopecia with hair regrowth of less than 50 percent of the amount before chemotherapy.

203. ~~185.~~ In addition, and as detailed above, Dr. Tallon's 2010 article concluded that, when a cocktail of Taxotere, Trastuzumab, and Carboplatin was administered and there was resulting permanent alopecia, Taxotere was the implicated agent. Its reasoning was that there was a lack of evidence linking alopecia with Trastuzumab and limited exposure to Carboplatin. Trastuzumab does not contain a component that causes hair loss and does not increase the rate of hair loss when combined with standard chemotherapy. Similarly, Carboplatin causes only mild temporary alopecia in 5 percent of users.

204. ~~186.~~ Likewise, the 2012 study by Dr. Kluger and others concluded that Taxanes were responsible for permanent scalp alopecia among patients who were administered a sequential regimen of FEC (fluorouracil, epirubicin, and cyclophosphamide) followed by docetaxel. They noted that no patients treated with only anthracycline regimens (and not docetaxel) suffered from permanent severe scalp alopecia.

205. ~~187.~~ Further, Drs. Thorp, Swift, Arundell and Wong in their 2014 presentation reported that 15.8 percent of Taxotere patients surveyed had significant persistent scalp hair loss for up to 3.5 years following completion of chemotherapy.

206. ~~188.~~ Finally, Sanofi's change to the Taxotere label in ~~2015~~, 2015 and 2018, described above, acknowledges that Taxotere causes permanent hair loss but fails to do so adequately. Moreover, some Defendants have chosen not to adopt Sanofi's revised labeling. Under the "Patient Counseling Information" of the revised label, the new text reads: "Explain to patients that side effects such as ... hair loss (cases of permanent hair loss have been reported) are associated with docetaxel administration." Additionally, under "Patient Information," the label states that the "most common side effects of TAXOTERE include: ... hair loss: in most cases normal hair growth should return. In some cases (frequency not known) permanent hair loss has been observed." The label contains no mention of irreversible or permanent hair loss under "Warnings and Precautions" or "Adverse

Reactions.”

207. ~~189.~~ By contrast, in a report issued on Taxotere on May 12, 2016, the European Medicines Agency (“EMA”) concluded that “[b]ased on review of the Sanofi global pharmacovigilance database, worldwide scientific literature, clinical studies, and biological plausibility, the cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.”

208. ~~190.~~ Because NDA holders and their assigns or agents are held to the knowledge of an expert in the field concerning the products they sell, Defendants cannot plead ignorance of the scientific information publicly available or otherwise available to them that would have supported a label change, including the studies and information discussed herein.

E. ~~V.~~ Sanofi Marketed & Promoted Taxotere Despite Knowing It Caused Permanent Alopecia

209. ~~191.~~ Sanofi, including its predecessors and affiliates, have designed, directed, and/or engaged in a marketing scheme to over promote Taxotere directly to consumers and for off-label uses not approved by the FDA. As a result, Sanofi has earned in excess of €7 billion in revenue on its sales of Taxotere in the United States:

Year	U.S. Sales as Reported by Sanofi S.A.
2000	€367,000,000
2001	€541,000,000
2002	€701,000,000
2003	€733,000,000
2004	Could not be located
2005	€695,000,000
2006	€708,000,000
2007	€691,000,000
2008	€737,000,000
2009	€827,000,000
2010	€786,000,000
2011	€243,000,000
2012	€53,000,000

2013	€42,000,000
2014	€8,000,000
2015	€-1,000,000
2016	€4,000,000
Total	€7,135,000,000

210. ~~192.~~ In or around 2000, Sanofi hired a marketing firm to conduct a study on the primary concerns of oncologists and breast cancer patients undergoing treatment. The results of the study revealed that breast cancer patients felt an innate need to stay ‘connected’ through various means.

211. ~~193.~~ As a result of the marketing study, Sanofi launched a new sales promotional campaign in 2000 known as “Connection Cards” in which gift packages were offered to breast cancer patients at their oncologist’s office. These gift packages initially included ten custom designed note cards and envelopes; a 30-minute prepaid long-distance calling card; a reference card with contact information for nationally recognized breast cancer organizations; a reference card with contact information with the company’s breast cancer support program; and most importantly, a brochure giving detailed information about Taxotere.

212. ~~194.~~ To maintain the effectiveness of the promotional campaign, Sanofi added coupons for wigs and vouchers for discounted taxi services to the gift packages provided to breast cancer patients. In 2002, Sanofi made available to U.S. patients approximately 60,000 “Connection Cards” through 150 sales representatives.

213. ~~195.~~ Sanofi claimed the promotional campaign to be a success, adding the campaign to its permanent rotation of promotional materials.

214. ~~196.~~ Sanofi also promoted Taxotere for the following breast cancer treatments, which at the time, were neither approved by the FDA nor supported by the available drug compendia: adjuvant breast cancer, neo-adjuvant breast cancer, weekly dose for metastatic breast cancer.

215. ~~197.~~ Sanofi directed its U.S. sales force to misrepresent the safety and effectiveness of

the off-label use of Taxotere to expand the market for Taxotere in unapproved settings, such as a first-

line of treatment or for early-stage breast cancer.

216. ~~198.~~ On July 26, 2001, the FDA's Division of Drug Marketing, Advertising and Communications, now known as the Office of Prescription Drug Promotion, sent a letter to Sanofi identifying promotional activities that were in violation of the FDCA and its implementing regulations on off-label promotion.

217. ~~199.~~ In particular, FDA identified promotional brochures distributed at the American Society of Clinical Oncology Annual Meeting in May 2001 that stated that Taxotere was safe and effective for first-line treatment in combination with Adriamycin such as that it was "the only taxane combination approved for first-line treatment of locally advanced or metastatic breast cancer."

218. ~~200.~~ This was considered off-label promotion because Taxotere in combination with Adriamycin was approved by FDA only for second-line treatment—not first-line treatment—of locally advanced or metastatic breast cancer. Likewise, as explained by FDA, other taxane combinations, as well as other classes of drug combinations, were approved for this first-line treatment. FDA demanded that Sanofi "immediately cease the distribution of these and similar promotional materials."

219. ~~201.~~ FDA sent a second warnings letter to Sanofi on December 18, 2002, concerning promotional materials at the 2002 Annual Meeting, which featured queen chess pieces and stated that Taxotere was "at the center of more strategies every day." According to FDA, these promotional materials constituted "false or misleading promotion" which could "compromise patient survival and safety." FDA focused on Sanofi's claim that Taxotere resulted in "significant survival advantages," noting that this statement was not supported by clinical trial results. FDA also noted that Sanofi underemphasized information concerning severe risks that can result from using

Taxotere.

220. ~~202.~~ Sanofi responded to FDA on December 30, 2002, stating “we are discontinuing the use of these [ads], and any similar materials.” Nonetheless, Sanofi continued its false and misleading promotional and marketing activities.

221. ~~203.~~ Despite Sanofi’s assurances that these and similar promotional materials would be discontinued and destroyed, FDA sent Sanofi a third warnings letter on July 17, 2003, identifying two direct-to-consumer promotional pieces that raised “similar” concerns. These two promotional ads appeared on the back of People Magazine's circulation wrap and prominently featured the slogan “The Next Move May Be the Key to Your Survival” and “It's Your Move,” which again featured the queen and chess piece theme.

222. ~~204.~~ FDA found these ads to be misleading because the headline suggests that, if cancer patients want to survive breast or lung cancer, their “next move” should include Taxotere, thus implying that Taxotere is “more effective than has been demonstrated by substantial evidence or substantial clinical experience.” FDA concluded that Sanofi’s ads “reinforce[] the message that treatment with Taxotere will result in significant survival advantages,” when the clinical data “did not necessarily represent longterm survival or a cure.” FDA demanded that Sanofi submit a letter stating the status of these items (active or discontinued) as well a list of violative promotional materials.

223. ~~205.~~ Sanofi replied on August 1, 2003, assuring FDA that the two ads had been discontinued and identifying another direct-to-consumer promotional piece, similar to the two ads. The third ad, which featured the same Taxotere slogans, “*The Next Move May Be the Key to Your Survival,*” and “*It's Your Move,*” had been disseminated in “Coping,” “MAAM,” and “Cure” Magazines between March and July 2003 and was planned to be disseminated in these magazines in addition to “Y-Me” magazine through December 2003. Only after follow-up telephone calls did Sanofi assure FDA in an August 21, 2003 letter that it had discontinued use of this additional

misleading piece.

224. ~~206.~~ FDA concluded on November 12, 2003 that these three ads likewise “misleadingly overstate[d] the survival benefits ... and impl[ie]d that survival depends on treatment with Taxotere,” while simultaneously “minimizing the serious and potentially life-threatening risks associated with

the drug.”

225. ~~207.~~ As late as January 2004, Sanofi distributed banned materials to physicians and other healthcare providers that promoted Taxotere, using materials with the same misleading slogans and substantially similar misleading information.

226. ~~208.~~ In addition, Sanofi’s salespeople were directed to “cherry pick” positive clinical study results. For example, in the breast cancer setting, Sanofi trained its salespeople to downplay the results of clinical trial results and the NIH Guidelines for Adjuvant Breast Cancer, which showed that evidence of taxanes’ role in the adjuvant treatment of node positive breast cancer was inconclusive. By contrast, to emphasize Taxotere’s superiority over Taxol, they were also instructed to highlight preliminary results and abstracts from weaker trials. Similarly, they were trained to emphasize the lower incidence of non-lethal side effects when compared with Taxol while omitting the lethal side effect of severe neutropenia that occurs more frequently when using Taxotere.

227. ~~209.~~ In doing so, Sanofi continued to make false and misleading statements promoting the “superior efficacy” of Taxotere over the competing product paclitaxel (Taxol). In June 2008, Sanofi utilized marketing and promotional materials for Taxotere at the annual meeting for the American Society of Clinical Oncology, comparing the efficacy of Taxotere versus paclitaxel (Taxol). Specifically, Sanofi utilized a “reprint carrier,” citing a clinical study published in the August 2005 edition of the Journal of Clinical Oncology. The cover of the reprint carrier claimed, among other

things: =

- “Taxotere demonstrated efficacy benefits vs paclitaxel”
- “This phase III study demonstrated that docetaxel is superior to paclitaxel in TTP, response duration, and OS [overall survival].”
- “Phase III trial demonstrated improved survival for Taxotere vs paclitaxel in metastatic breast cancer”

229. 228. ~~210.~~ Sanofi’s statements in the “reprint carrier” marketing the conclusions of the 2005 Journal of Clinical Oncology study were false and/or misleading in light of the 2007 and 2008 studies finding that Taxotere was not more effective than paclitaxel (Taxol) in the treatment of breast cancer.

230. ~~211.~~ Specifically, in August 2007, Cancer Treatment Reviews published a study that found no significant differences in the efficacy and outcomes obtained with Taxotere or Taxol (paclitaxel) in breast cancer treatment. Likewise, a 2008 study in the New England Journal of Medicine concluded that Taxol (paclitaxel) was more effective than Taxotere for patients undergoing standard adjuvant chemotherapy with doxorubicin and cyclophosphamide.

231. ~~212.~~ As a result of these false and misleading statements, in 2009, the FDA issued a warning letter to Sanofi citing these unsubstantiated claims of superiority over paclitaxel stating:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional reprint carrier [US.DOC.07.04.078] for Taxotere (docetaxel) Injection Concentrate, Intravenous Infusion (Taxotere) submitted under cover of Form FDA 2253 by Sanofi-Aventis (SA) and obtained at the American Society of Clinical Oncology annual meeting in June 2008. The reprint carrier includes a reprint from the Journal of Clinical Oncology, which describes the TAX 311 study. This reprint carrier is false or misleading because it presents unsubstantiated superiority claims and overstates the efficacy of Taxotere. Therefore, this material misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) and 321(n). Cf. 21 CFR 202.1(e)(6)(i), (ii) & (e)(7)(ii).

...

The reference cited in support of these claims ... does not constitute substantial evidence or substantial clinical experience to support these claims and representations because, among other factors, the study failed to demonstrate statistical significance on the primary endpoint and has not been replicated.

232. ~~213.~~ In addition, Sanofi also began indirectly promoting Taxotere through a series of

direct- to-consumer television commercials that began airing in 2007. One of these commercials showed breast cancer patients slowly removing their wigs as an omniscient voice stated: “Cancer is tough but so are you. Get the facts, share the feelings, look to the future—Sanofi Aventis— because health matters and so do you.” These and other similar direct-to-consumer advertisements continued at least through 2010.

E. Sanofi Actively Sought to Hide that Taxotere Could Cause Permanent Hair Loss

233. Sanofi’s marketing efforts also affirmatively sought to minimize any association between Taxotere and permanent alopecia.

234. According to Sanofi’s Global Safety Officer for Taxotere, Sanofi knew that Taxotere could cause permanent hair loss in 2006. Despite this, Sanofi created and published in 2006 an information brochure for oncology nurses that described alopecia as “a common, yet temporary, side effect of some cancer medicines” and provided no information regarding the risk of permanent alopecia associated with Taxotere.

235. In addition, in 2010, Sanofi began proactively removing any comments about permanent alopecia from its Facebook page titled “Voices,” which Sanofi sponsored for the alleged purpose of “mak[ing] Voices heard throughout the community on issues of importance to patients...”

236. Sanofi began this practice after it observed posts from women about permanent alopecia following a March 5, 2010 article in the Globe and Mail, which described instances of permanent hair loss among Taxotere patients. In response, Sanofi’s communications department formed a Rapid Response Team, and among its responsibilities included monitoring Sanofi’s Voices Facebook page at all times to remove any posts about Taxotere and permanent hair loss.

237. Sanofi shortly thereafter hired an outside company, InTouch Solutions, to conduct this around-the-clock monitoring of its Facebook page. At Sanofi’s direction, InTouch logged and

removed posts about permanent hair loss, blocked the user posting about it, and reported the user to Facebook to have her banned from the platform.

238. For example, one Facebook user posted on Sanofi's page the following: "When will you inform oncologists that there is a problem with your chemo drug, Taxotere? Why don't you want women to know they could be left permanently disfigured? Because they will choose a different drug not made by you. The net is closing in on you, Sanofi." At Sanofi's direction, InTouch Solutions removed the post within an hour, blocked the user from posting on the page, and reported the user to Facebook.

239. Another user posted, "My medical team have spoken to you, and therefore I have been informed that YOUR DRUG Taxotere has done this to me. Why do you ignore me and REFUSE to contact me? Why don't you explain to me why your drug Taxotere has permanently disfigured me and hundreds of others?" InTouch Solutions removed the post within an hour and reported the user to Facebook. The same user posted 28 more times, and at Sanofi's direction, InTouch Solutions removed the post from Facebook and had the woman permanently banned from the page.

240. A different user posted "I did say I wouldn't stop until there was global publicity. You can't shut up women that you disfigure." Her post was removed by InTouch Solutions within an hour.

241. After successfully scrubbing mention of permanent hair loss from Sanofi's Voices Facebook page, InTouch Solutions created a presentation to market its services to other drug companies, and it used the "crisis management" services it provided to Sanofi as a case study of what it could accomplish for its clients.

242. As a result of Sanofi's fraudulent concealment of the association between Taxotere

and Permanent Chemotherapy Induced Alopecia, the medical community and patients, including Plaintiffs, were deprived of adequate information about the drug. Consequently, Plaintiffs were unaware of the connection between their use of Taxotere and their injury of permanent hair loss.

G. ~~VI.~~Permanent Alopecia is Devastating for Plaintiffs.

243. ~~214.~~Research indicates that a majority of women consider alopecia the most traumatic side effect of cancer treatment. One study states that 58 percent of women preparing for chemotherapy describe alopecia as the most disturbing anticipated side effect, and that 8 percent of women may choose to forego treatment based on possible alopecia. Although baldness is the most commonly recognized form of alopecia, chemotherapy-related hair loss can extend to eyebrows, eyelashes, arm and leg hair, pubic hair, etc.

244. ~~215.~~Women with cancer who experience alopecia, as compared with women with cancer who do not, report lower self-esteem, poorer body image, and a lower quality of life. Alopecia can be stigmatizing and may result in anger, anxiety, embarrassment, sadness, depression, shame, helplessness, fear, and loss of sense of self. Women with alopecia may experience a loss of sense of femininity, sexuality, attractiveness, self-confidence, and womanhood. Even if hair does grow back, studies have found that these negative thoughts and feelings remain; body image tends not to return to pre-treatment levels.

245. ~~216.~~Alopecia also alters how women interact with others and experience social situations.

Alopecia symbolizes cancer identity and treatment, even when individuals wear wigs or garments to cover the hair loss. These symbols can heighten an individual's everyday awareness that she has or had cancer.

246. ~~217.~~Hair loss alters how women recognize themselves and how others interact with them.

Hair is a critical aspect of appearance that can facilitate recognition as female, young, and healthy. By contrast, loss of hair may cause others to categorize individuals as old and unhealthy. As a result, women who suffer from alopecia have a heightened awareness of their appearance during social interactions, and may be treated differently than they were before their hair loss.

247. ~~218.~~To cope, many avoid social situations because they are nervous that others will treat them differently. These fears are not unfounded. In one study of cancer survivors, 75 percent of participants reported experiencing silent stares from others that they attributed to their “cancer appearance.” Participants also reported that people they knew avoided public contact with them.

248. ~~219.~~Hair loss can also increase risk of injury to the body. Nose hair, eyelashes, ear hair, etc. serve important bodily functions and are necessary for the protection against injury to organs critical to human senses. Hair loss in these areas places women at risk of permanent injuries.

249. ~~220.~~Even when, unlike here, patients were warned that cancer-related hair loss may occur,

cancer patients have reported feeling that they were not given adequate information about how to manage cancer-related hair loss. This underscores the importance of healthcare providers appreciating the traumatic effect that cancer-related alopecia may have on their patients.

FIRST CLAIM FOR RELIEF
(Strict Products Liability – Failure to Warn – Against All Defendants)

250. ~~221.~~Plaintiffs incorporate by reference each and every paragraph of this ~~Second~~Third Amended Master Complaint as if fully set forth herein and further allege as follows.

251. ~~222.~~At all relevant times, Defendants were in the business of designing, researching, manufacturing, testing, promoting, marketing, selling, and/or distributing pharmaceutical products, including the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate as hereinabove described that was used by Plaintiffs, or have recently acquired the entities that did the same.

252. ~~223.~~The Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate designed, formulated, produced, manufactured, sold, marketed, distributed, supplied and/or placed into the stream of commerce by Defendants failed to provide adequate warnings to users and their healthcare providers, including Plaintiffs and Plaintiffs’ healthcare providers, of the risk of side effects associated with the use of Taxotere, Docetaxel Injection, Docetaxel Injection

Concentrate, and Docefrez, particularly the risk of developing disfiguring, permanent alopecia.

253. ~~224.~~ As the holder of the Reference Listed Drug (“RLD”) for Taxotere, Sanofi supplied the labeling for Winthrop U.S.’s generic version of Taxotere.

254. ~~225.~~ The Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate designed, formulated, produced, manufactured, sold, marketed, distributed, supplied and/or placed into the stream of commerce by Defendants and ultimately administered to Plaintiffs lacked such warnings when it left Defendants’ control.

255. ~~226.~~ The risks of developing disfiguring, permanent alopecia were known to or reasonably scientifically knowable by Defendants at the time the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate left Defendants’ control.

256. ~~227.~~ Any warnings actually provided by Defendants did not sufficiently and/or accurately reflect the symptoms, type, scope, severity, and/or duration of these side effects, particularly the risks of developing disfiguring, permanent alopecia.

257. ~~228.~~ Without adequate warning of these side effects, Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate are not reasonably fit, suitable, or safe for its reasonably anticipated or intended purposes.

258. ~~229.~~ Plaintiffs were reasonably foreseeable users of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate who used the drug in reasonably anticipated manners.

259. ~~230.~~ Plaintiffs would not have used Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate had they (and their Physicians) been provided an adequate warning by Defendants of the risk of these side effects.

260. ~~231.~~ As a direct and proximate result of Defendants’ failure to warn of the potentially severe adverse effects of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, Plaintiffs suffered and continue to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic

damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counseling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and impairment of the quality and enjoyment of life.

SECOND CLAIM FOR RELIEF

(Strict Products Liability for Misrepresentation – Against All Defendants)

261. ~~232.~~ Plaintiffs incorporate by reference each and every paragraph of this ~~Second~~ Third Amended Master Complaint as if fully set forth herein and further allege as follows.

262. ~~233.~~ Defendants sold the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate that Plaintiffs' healthcare providers prescribed for Plaintiffs and that Plaintiffs used.

263. ~~234.~~ Defendants were engaged in the business of selling the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate for resale, use, or consumption.

264. ~~235.~~ Defendants misrepresented facts as set forth herein concerning the character or quality of the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate that would be material to potential prescribers and purchasers or users of the product.

265. ~~236.~~ Defendants' misrepresentations were made to potential prescribers and/or purchasers or users as members of the public at large.

266. ~~237.~~ As purchasers or users, Plaintiffs and/or their healthcare providers reasonably relied on the misrepresentations.

267. ~~238.~~ Plaintiffs were persons who would reasonably be expected to use, consume, or be affected by the Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez.

268. ~~239.~~ As a result of the foregoing acts and omissions, Defendants caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counselling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and

past, present, and future loss and impairment of the quality and enjoyment of life.

THIRD CLAIM FOR RELIEF **(Negligence – Against All Defendants)**

269. ~~240.~~ Plaintiffs incorporate by reference each and every paragraph of this ~~Second~~ Third Amended Master Complaint as if fully set forth herein and further allege as follows.

270. ~~241.~~ Defendants had a duty to exercise reasonable care in the design, research, formulation, manufacture, production, marketing, testing, supply, promotion, packaging, sale, and/or distribution of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, including a duty to assure that the product would not cause users to suffer unreasonable, disfiguring, and dangerous side effects.

271. ~~242.~~ Defendants breached these duties when they put Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate into interstate commerce, unreasonably and without adequate and/or proper warning to Plaintiffs and their healthcare providers, a product that Defendants knew or should have known created a high risk of unreasonable, disfiguring, and dangerous side effects.

272. ~~243.~~ The negligence of Defendants, their agents, servants, and/or employees, included

but was not limited to, the following acts and/or omissions:

- (a) Manufacturing, producing, promoting, formulating, creating, and/or designing Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate without thoroughly, adequately, and/or sufficiently testing it—including pre-clinical and clinical testing and post-marketing surveillance—for safety and fitness for use and/or its dangers and risks;
- (b) Marketing Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate to Plaintiffs, Plaintiffs' healthcare providers, the public, and the medical and healthcare professions without adequately and correctly warning and/or disclosing the existence, severity, and duration of known or knowable side effects, including permanent alopecia;
- (c) Marketing Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate to Plaintiffs, Plaintiffs' healthcare providers, the public, and the medical and healthcare professions without providing adequate instructions regarding safety precautions to be observed by users, handlers, and persons who would reasonably and foreseeably come into contact with, and more particularly, use, Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez;
- (d) Advertising and recommending the use of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez; without sufficient knowledge of its safety profile;
- (e) Representing to Plaintiffs, Plaintiffs' healthcare providers, the public, and the medical and healthcare professions that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were superior to other commercially available products designed to treat the same forms of cancer Taxotere was designed to treat, when in fact they were not;
- (f) Designing, manufacturing, producing, and/or assembling Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate in a manner that was dangerous to its users;
- (g) Concealing information from Plaintiffs, Plaintiffs' healthcare providers, the public, other medical and healthcare professionals, and the FDA that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were unsafe, dangerous, and/or non-conforming with FDA regulations;
- (h) Concealing from and/or misrepresenting information to Plaintiffs, Plaintiffs' healthcare providers, other medical and healthcare professionals, and/or the FDA concerning the existence and severity of risks and dangers of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, as compared to other forms of treatment for cancer.; and
- (i) Encouraging the sale of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, either directly or indirectly, orally or in writing, to

Plaintiffs and Plaintiffs' healthcare providers without warning about the need for more comprehensive and regular medical monitoring than usual to ensure early discovery of potentially serious side effects.

273. ~~244.~~ Despite the fact that Defendants knew or should have known that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate caused unreasonably dangerous side effects, Defendants continued and continue to market, manufacture, distribute, and/or sell Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate to consumers, including Plaintiffs.

274. ~~245.~~ Plaintiffs and Plaintiffs' healthcare providers were therefore forced to rely on safety information that did not accurately represent the risks and benefits associated with the use of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate as compared to other products

already commercially available to treat the same types of cancer Taxotere was designed to treat.

275. ~~246.~~ Defendants knew or should have known that consumers such as Plaintiffs would use their product and would foreseeably suffer injury as a result of Defendants' failure to exercise reasonable care, as set forth above.

276. ~~247.~~ Defendants' negligence was a proximate cause of Plaintiffs' injuries, harms, damages, and losses, in connection with the use of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, including but not limited to: past and future medical expenses; psychological counseling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement including permanent and irreversible alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and impairment of the quality and enjoyment of life.

FOURTH CLAIM FOR RELIEF **(Negligent Misrepresentation – Against All Defendants)**

277. ~~248.~~ Plaintiffs incorporate by reference each and every paragraph of this ~~Second~~ Third Amended Master Complaint as if fully set forth herein and further allege as follows.

278. ~~249.~~ Defendants had a duty to represent to Plaintiffs, Plaintiffs' healthcare providers, the medical and healthcare community, and the public in general that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate had been tested and found to be safe and effective for the treatment of various forms of cancer.

279. ~~250.~~ When warning of safety and risks of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, Defendants negligently represented to Plaintiffs, Plaintiffs' healthcare providers, the medical and healthcare community, and the public in general that they had been tested and was found to be safe and/or effective for its indicated use.

280. ~~251.~~ Defendants concealed their knowledge of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, defects from Plaintiffs, Plaintiffs' healthcare providers, and the public in general and/or the medical community specifically.

281. ~~252.~~ Defendants concealed their knowledge of the defects in their products from Plaintiffs, Plaintiffs' healthcare providers, and the public in general.

282. ~~253.~~ Defendants misrepresented the novel nature of their product in order to gain a market advantage resulting in billions of dollars in revenues at the expense of vulnerable cancer victims such as Plaintiffs.

283. ~~254.~~ Defendants made these misrepresentations with the intent of defrauding and deceiving Plaintiffs, Plaintiffs' healthcare providers, the public in general, and the medical and healthcare community in particular, and were made with the intent of inducing Plaintiffs, Plaintiffs' healthcare providers, the public in general, and the medical community in particular, to recommend, dispense, and/or purchase Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate for use in the treatments of various forms of cancer, including, but not limited to, breast cancer.

284. ~~255.~~ Defendants failed to exercise ordinary and reasonable care in their representations of Taxotere while involved in its manufacture, sale, testing, quality assurance, quality control, and/or distribution into interstate commerce, and Defendants negligently misrepresented Taxotere's, Docetaxel Injection's, Docetaxel Injection Concentrate's, and Docefrez's high risks of unreasonable, dangerous side effects.

285. ~~256.~~ Defendants breached their duty in misrepresenting Taxotere's, Docetaxel Injection's, Docetaxel Injection Concentrate's, and Docefrez's, serious side effects to Plaintiffs, Plaintiffs' healthcare providers, the medical and healthcare community, the FDA, and the public in general.

286. ~~257.~~ Plaintiffs and Plaintiffs' healthcare providers reasonably relied on Defendants to fulfil

their obligations to disclose all facts within their knowledge regarding the serious side effects of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez.

287. ~~258.~~ As a result of the foregoing acts and omissions, Defendants caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counselling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and impairment of the quality and enjoyment of life.

FIFTH CLAIM FOR RELIEF

(Fraudulent Misrepresentation – Against All Defendants)

288. ~~259.~~ Plaintiffs incorporate by reference each and every paragraph of this ~~Second~~ Third Amended Master Complaint as if fully set forth herein and further allege as follows.

289. ~~260.~~ Defendants represented to Plaintiffs, Plaintiffs' healthcare providers, the medical and healthcare community, and the public in general that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate had been tested and was found to be safe and effective for the treatment of certain forms of cancer and was free of defects that could and would cause serious side effects, including permanent and irreversible hair loss.

290. ~~261.~~ Defendants fraudulently omitted from these representations information that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate could and did cause serious side effects, including permanent and irreversible hair loss.

291. ~~262.~~ These representations were material and false.

292. ~~263.~~ Defendants made these representations and omissions:

- (a) with knowledge or belief of their falsity, and/or in the case of omissions, with knowledge or belief of falsity of the resulting statements;
- (b) positively and recklessly without knowledge of their truth or falsity;
- (c) with knowledge that they were made without any basis; and/or
- (d) without confidence in the accuracy of the representations or statements resulting from the omissions.

293. ~~264.~~ Defendants made these false representations with the intention or expectation that Plaintiffs, Plaintiffs' healthcare providers, the public in general, and the medical community in particular, would recommend, dispense, and/or purchase Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate for use in the treatments of various forms of cancer, including, but not limited to, breast cancer, all of which evidenced a callous, reckless, willful, wanton, and depraved indifference to the health, safety, and welfare of Plaintiffs.

294. ~~265.~~ At the time Defendants made the aforesaid representations, and, at the time Plaintiffs used Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, Plaintiffs and Plaintiffs' healthcare providers were unaware of the falsity of Defendants' representations, statements and/or implications and justifiably and reasonably relied upon Defendants' representations, statements, and implications, believing them to be true.

295. ~~266.~~ In reliance upon Defendants' representations, Plaintiffs and Plaintiffs' healthcare providers were induced to and did use and prescribe Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, which caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counseling and therapy expenses; past and future loss of earnings; past and

future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and

future physical and mental pain, suffering, and discomfort; and past, present, and future loss and

impairment of the quality and enjoyment of life.

SIXTH CLAIM FOR RELIEF
(Fraudulent Concealment – Against All Defendants)

296. ~~267.~~ Plaintiffs incorporate by reference each and every paragraph of this ~~Second~~Third Amended Master Complaint as if fully set forth herein and further allege as follows.

297. ~~268.~~ At all times during the course of dealing between Defendants and Plaintiffs and Plaintiffs' healthcare providers, Defendants misrepresented the design characteristics and safety of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate for their intended use.

298. ~~269.~~ Defendants knew or were reckless in not knowing that its representations were false.

299. ~~270.~~ In representations made to Plaintiffs and Plaintiffs' healthcare providers, Defendants fraudulently concealed and intentionally omitted the following material information:

- (a) that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were not as safe as other forms of treatment for which they were marketed and sold to cancer patients;
- (b) that the risks of adverse events with Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were higher than those with other forms of treatment for which they were marketed and sold to cancer patients;
- (c) that the risks of adverse events with Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were not adequately tested and/or known by Defendants;
- (d) that Defendants were aware of dangers in Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, in addition to and above and beyond those associated with other forms of treatment for cancer patients;
- (e) that Taxotere, Docefrez, Docetaxel Injection, Docetaxel Injection Concentrate, and Docetaxel Injection Concentrate were defective in that it caused dangerous side effects as well as other severe and permanent health consequences in a much more and significant rate than other forms of treatment for cancer patients;

300. ~~271.~~ Defendants had a duty to disclose to Plaintiffs and Plaintiffs' healthcare providers the defective nature of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, including, but not limited to, the heightened risks of disfiguring, permanent alopecia.

301. ~~272.~~ Defendants had sole access to material facts concerning the defective nature of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate and their propensity to cause serious and dangerous side effects, and therefore cause damage to persons who used the drugs at issue, including Plaintiffs, in particular.

302. ~~273.~~ Defendants' concealment and omissions of material fact concerning the safety of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were made purposefully, wilfully, wantonly, and/or recklessly to mislead Plaintiffs and Plaintiffs' healthcare providers into reliance on the continued use of the drugs and to cause them to purchase, prescribe, and/or dispense Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate and/or use them.

303. ~~274.~~ Defendants knew that Plaintiffs and Plaintiffs' healthcare providers had no way to determine the truth behind Defendants' concealment and omissions, including the material omissions of fact surrounding Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate set forth herein.

304. ~~275.~~ Plaintiffs and Plaintiffs' healthcare providers reasonably relied on information revealed by Defendants that negligently, fraudulently, and/or purposefully did not include facts that were concealed and/or omitted by Defendants.

305. ~~276.~~ As a result of the foregoing acts and omissions, Defendants caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counseling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and

past, present, and future loss and impairment of the quality and enjoyment of life.

SEVENTH CLAIM FOR RELIEF
(Fraud and Deceit – Against All Defendants)

306. ~~277.~~ Plaintiffs incorporate by reference each and every paragraph of this ~~Second~~Third Amended Master Complaint as if fully set forth herein and further allege as follows.

307. ~~278.~~ Defendants committed fraud by omission in applying for and gaining patent protection for Taxotere resulting in increased sales and market penetration. This increased market penetration was the proximate cause of Plaintiffs' exposure to the side effects of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez.

308. ~~279.~~ Defendants fraudulently claimed superior efficacy over other products designed to treat the same conditions for which Taxotere was designed to treat. These fraudulent representations were the proximate cause of Plaintiffs' exposure to the side effects of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez.

309. ~~280.~~ As a result of Defendants' research and testing, or lack thereof, Defendants intentionally distributed false information, including, but not limited to, assuring Plaintiffs, Plaintiffs' healthcare providers and/or the public that Taxotere, Docefrez, Docetaxel Injection, or Docetaxel Injection Concentrate was safe and effective for use in the treatment of various forms of cancer, including breast cancer.

310. ~~281.~~ As a result of Defendants' research and testing, or lack thereof, Defendants intentionally omitted certain results of testing and or research to Plaintiffs, Plaintiffs' healthcare providers, healthcare professionals, and/or the public.

311. ~~282.~~ Defendants had a duty when disseminating information to Plaintiffs, Plaintiffs' healthcare providers, and the public to disseminate truthful information.

312. ~~283.~~ Defendants had a duty when disseminating information to Plaintiffs, Plaintiffs'

healthcare providers, and the public not to deceive Plaintiffs, Plaintiffs' healthcare providers, and/or

the public.

313. ~~284.~~The information Defendants distributed to Plaintiffs, Plaintiffs' healthcare providers, and the public, including, but not limited to, reports, press releases, advertising campaigns, and other forms of media contained material misrepresentations of fact and/or omissions.

314. ~~285.~~The information Defendants distributed to Plaintiffs, Plaintiffs' healthcare providers, and the public intentionally included false representations that Defendants' drug Taxotere was safe and effective for the treatment of various forms of cancer, including breast cancer.

315. ~~286.~~The information Defendants distributed to Plaintiffs, Plaintiffs' healthcare providers, and the public intentionally included false representations that Defendants' drug Taxotere, Docefrez, Docetaxel Injection, or Docetaxel Injection Concentrate carried the same risks, hazards, and/or dangers as other forms of treatment for the same conditions for which Taxotere was designed to treat.

316. ~~287.~~The information Defendants distributed to Plaintiffs, Plaintiffs' healthcare providers, and the public intentionally included false representations that Taxotere was not injurious to the health and/or safety of its intended users.

317. ~~288.~~The information Defendants distributed to Plaintiffs, Plaintiffs' healthcare providers, and the public intentionally included false representations that Taxotere was no more injurious to the health and/or safety of its intended users as other forms of cancer treatments for which Taxotere was designed to treat.

318. ~~289.~~These representations by Defendants were all false and misleading.

319. ~~290.~~Defendants intentionally suppressed, ignored, and disregarded test results not favorable to Defendants and that demonstrated Taxotere was not safe as a means of treatment for certain types of cancer for which Taxotere was designed to treat.

320. ~~291.~~Defendants intentionally made material misrepresentations to Plaintiffs, Plaintiffs'

healthcare providers, and the public in general, including the medical profession, regarding the safety of Taxotere, specifically, but not limited to, Taxotere not having dangerous and serious health and/or safety concerns.

321. ~~292.~~ Defendants intentionally made material misrepresentations to Plaintiffs, Plaintiffs' healthcare providers, and the public in general, including the medical profession, regarding the safety of Taxotere, specifically, but not limited to, Taxotere being as safe as other products designed to treat the same conditions Taxotere was designed to treat.

322. ~~293.~~ It was Defendants' intent and purpose in making these false representations to deceive and defraud Plaintiffs, Plaintiffs' healthcare providers, and/or the public and to gain the confidence of Plaintiffs, Plaintiffs' healthcare providers, the public, and/or healthcare professionals to falsely ensure the quality and fitness for use of Taxotere and induce Plaintiffs, Plaintiffs' healthcare providers, and the public, including the medical profession, to purchase, request, dispense, prescribe, recommend, and/or continue to use Taxotere.

323. ~~294.~~ Defendants made the aforementioned false claims and false representations with the intent of convincing Plaintiffs, Plaintiffs' healthcare providers, the public, and/or healthcare professionals that Taxotere, Docefrez, Docetaxel Injection, or Docetaxel Injection Concentrate was fit and safe for use as treatment for certain types of cancer, including breast cancer.

324. ~~295.~~ Defendants made the aforementioned false claims and false representations with the intent of convincing Plaintiffs, Plaintiffs' healthcare providers, the public, and/or healthcare professionals that Taxotere was fit and safe for use as treatment for certain forms of cancer and did not pose risks, dangers, or hazards above and beyond those identified and/or associated with other forms of treatment for which Taxotere, Docefrez, Docetaxel Injection, or Docetaxel Injection Concentrate was designed to treat.

325. ~~296.~~ Defendants made false claims and false representations in its documents submitted to

Plaintiffs, Plaintiffs' healthcare providers, the public, and healthcare professionals that Taxotere did

not present risks related to disfigurement secondary to permanent alopecia.

326. ~~297.~~ Defendants made false claims and false representations in its documents submitted to Plaintiffs, Plaintiffs' healthcare providers, the public, and healthcare professionals that Taxotere, Docefrez, Docetaxel Injection, or Docetaxel Injection Concentrate did not present health and/or safety risks greater than other forms of treatment for the same conditions Taxotere was designed to treat.

327. ~~298.~~ Defendants made these and other representations with a pretense of actual knowledge when Defendants had no knowledge of the truth or falsity of these representations, and Defendants made these representations recklessly and without regard to the actual facts.

328. ~~299.~~ Defendants made these and other representations with the intention of deceiving and defrauding Plaintiffs and Plaintiffs' healthcare providers.

329. ~~300.~~ Defendants made these and other representations in order to induce Plaintiffs and Plaintiffs' healthcare providers to rely upon the misrepresentations.

330. ~~301.~~ Defendants' false misrepresentations caused Plaintiffs and/or Plaintiffs' healthcare providers to purchase, use, rely on, request, dispense, recommend, and/or prescribe Taxotere.

331. ~~302.~~ Defendants recklessly and intentionally falsely represented the dangerous and serious health and/or safety concerns of Taxotere to the public at large, and Plaintiffs and Plaintiffs' healthcare providers in particular, for the purpose of influencing the marketing of a product Defendants knew was dangerous and defective and/or not as safe as other alternatives, including other forms of treatment for cancer.

332. ~~303.~~ Defendants wilfully and intentionally failed to disclose, concealed, and/or suppressed the material facts regarding the dangerous and serious health and/or safety concerns related to Taxotere.

333. ~~304.~~ Defendants wilfully and intentionally failed to disclose the truth and material facts

related to Taxotere and made false representations with the purpose and design of deceiving and lulling Plaintiffs and Plaintiffs' healthcare providers into a sense of security so that Plaintiffs and Plaintiffs' healthcare providers would rely on Defendants' representations to purchase, use, dispense, prescribe, and/or recommend Taxotere.

334. ~~305.~~ Defendants, through their public relations efforts, which included, but were not limited to, public statements and press releases, knew or should have known that the public, including Plaintiffs and Plaintiffs' healthcare providers, would rely upon the information being disseminated.

335. ~~306.~~ Plaintiffs and/or Plaintiffs' healthcare providers did in fact rely on and believe Defendants' false representations to be true at the time they were made, and they relied upon Defendants' false representations and superior knowledge of how Taxotere would treat certain forms of cancer for which Taxotere was designed to treat.

336. ~~307.~~ At the time Defendants' false representations were made, Plaintiffs and/or Plaintiffs' healthcare providers did not know the truth and were not with reasonable diligence able to discover the truth with regard to the dangerous and serious health and/or safety concerns of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez.

337. ~~308.~~ Plaintiffs and their healthcare providers did not discover the true facts with respect to Defendants' false representations and the dangerous and serious health and/or safety concerns of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez, and Plaintiffs and their healthcare providers with reasonable diligence could not have discovered the true facts.

338. ~~309.~~ Had Plaintiffs and their healthcare providers known the true facts with respect to the dangerous and serious health and/or safety concerns of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez, Plaintiffs would not have purchased, used, and/or relied on Defendants' drug Taxotere.

339. ~~340.~~ Defendants' aforementioned conduct constitutes fraud and deceit, and it was

committed and/or perpetrated wilfully, wantonly, and/or purposefully on Plaintiffs.

340. ~~341.~~ As a result of the foregoing acts and omissions, Defendants caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counselling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and impairment of the quality and enjoyment of life.

EIGHTH CLAIM FOR RELIEF
(Breach of Express Warranty – Against Sanofi-Related Entities Only)

341. ~~342.~~ Plaintiffs incorporate by reference each and every paragraph of this ~~Second~~ Third Amended Master Complaint as if fully set forth herein and further allege as follows.

342. ~~343.~~ Defendants expressly warranted to Plaintiffs and Plaintiffs' healthcare providers that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were safe and fit for use for the purposes intended, that they did not produce any dangerous side effects in excess of those risks associated with other forms of treatment for cancer, that the side effects they did produce were accurately reflected in the warnings, and that they was adequately tested.

343. ~~344.~~ These express warranties became part of the basis of the bargain Defendants made with Plaintiffs.

344. ~~345.~~ Plaintiffs and their healthcare providers relied on Defendants' express warranties in electing to purchase and use their product.

345. ~~346.~~ Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate do

not conform to Defendants' express warranties, because is the drugs are not safe, were not adequately

tested, and have numerous serious side effects, which are in excess of those risks associated with other forms of treatment and which were not accurately warned about by Defendants.

346. ~~347.~~ Members of the medical community, including physicians and other healthcare providers, relied upon the representations and warranties of Defendants for use of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate in recommending, prescribing, and/or dispensing the drugs at issue.

347. ~~348.~~ Defendants knew or should have known that, in fact, their representations and warranties were false, misleading, and untrue.

348. ~~349.~~ As a direct and proximate result of the foregoing breaches of warranty, Defendants caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counseling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and impairment of the quality and enjoyment of life.

PRAYER FOR RELIEF

349. ~~320.~~ WHEREFORE, Plaintiffs pray for relief and judgement against each of the Defendants as appropriate to each cause of action alleged, as follows: compensatory damages and general damages in an amount that will conform to proof at time trial; special damages in an amount within the jurisdiction of this Court and according to proof at the time of trial; loss of earnings and

impaired earning capacity according to proof at the time of trial; medical expenses, past and future, according

to proof at the time of trial; for past and future mental and emotional distress, according to proof;

damages for loss of care, comfort, society, and companionship in an amount within the jurisdiction of this Court and according to proof; for punitive or exemplary damages according to proof; restitution, disgorgement of profits, and other equitable relief; attorneys' fees; for costs of suit incurred herein; for pre- and post-judgment interest as provided by law; and for such other and further relief as the Court may deem just and proper.

JURY DEMAND

350. ~~321.~~ Plaintiffs demand a trial by jury on all issues so triable.

Dated: October 8, 2018

Respectfully submitted,

Dated: September 27, 2018

Respectfully submitted,

/s/ Christopher L. Coffin

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CERTIFICATE OF SERVICE

I hereby certify that on ~~September 27, 2018,~~October 8, 2019, I electronically filed the foregoing with the Clerk of Court by using the CM/ECF system which will send a notice of electronic filing to all counsel of record who are CM/ECF participants.

/s/ M. Palmer Lambert
M. PALMER LAMBERT

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Input:	
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Description	2018.09.27 - MDL - 4407 Second Amended Master Long Form Complaint and Demand for Jury Trial (Pendley Baudin re all cases)
Document 2 ID	file:///C:/Users/psullivan/Desktop/TAXOTERE - Third Amended Master Compl 10.08.2019 (00377064xAD72D).pdf
Description	TAXOTERE - Third Amended Master Compl 10.08.2019 (00377064xAD72D)
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Moved from	2
Moved to	2

Style change	0
Format changed	0
Total changes	683

EXHIBIT B

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL) *
PRODUCTS LIABILITY * Docket No.: 16-MD-2740
LITIGATION * Section N
November 10, 2106
This Document Relates To All Cases * New Orleans, Louisiana
* * * * *

TRANSCRIPT OF MONTHLY STATUS CONFERENCE
HEARD BEFORE THE HONORABLE KURT D. ENGELHARDT
UNITED STATES DISTRICT JUDGE

APPEARANCES:

For the Plaintiffs:

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1 will --

2 THE COURT: Right. Okay.

3 MR. COFFIN: -- but I don't know of any at this
4 point.

5 THE COURT: Well, I'm just asking about as we sit
6 here today --

7 MR. COFFIN: No.

8 THE COURT: -- looking at the horizon of what we'll
9 have to deal with.

10 Insofar as -- you all have it on your list, and
11 I have it on mine as well -- a master complaint. We have done
12 that in the two MDLs that I have handled. I thought it was
13 very useful and productive to try to tee everything up on a
14 master complaint, which would bring up the Rule 12 motion
15 practice and some of the things that have already been filed in
16 some of the cases.

17 When we do get liaison counsel, I would like you
18 all to consider filing a master complaint. I'm not going to
19 order it, that it be filed by any particular day today. But I
20 think that is something that is going to need to be addressed
21 early on by liaison counsel.

22 So you certainly may begin discussing that and
23 what that might look like, what issues might be brought to the
24 fore in a master complaint, but I'd like to pursue that line of
25 thought. I take it you all have since it's on your list here,

1 **MR. STRONGMAN:** And I think a couple of issues that
2 are, again, what I would kind of consider hurdle issues in this
3 litigation involve -- you mentioned general causation, and it
4 is complicated. And I think this litigation is somewhat unique
5 in that specific and general causation are perhaps more balled
6 up together here than in other places.

7 For example, Taxotere, in most all of the cases
8 that we've seen to date that have been filed, involves
9 treatment with a host of chemotherapy agents. It's a
10 collection of medications that are used, all of which have hair
11 loss as a potential side effect.

12 So you have a very complicated set of facts with
13 each and every person. And so you're absolutely right, the
14 causation is a big hurdle, and specific causation is going to
15 be an even bigger hurdle.

16 All chemotherapy agents in general have hair
17 loss as a side effect. Everybody knows that. And we're going
18 to have this tug and pull, I believe, too, on, what is the
19 injury that we're talking about, what is permanent hair loss,
20 what is persistent hair loss, and how do we define that, which
21 is another critical issue. It has a scientific component to it
22 certainly, but it will also have a significant impact on how we
23 are able to kind of collectively evaluate our cases together as
24 well.

25 So I agree with you, that addressing those kind

1 of causation and scientific definitional issues are important
2 to understand how we can move this litigation forward.

3 **THE COURT:** Okay. Well, it was just a thought. It
4 was on my list of things that I would ask you all to consider.
5 It sounds like you both have, so we'll get into that in a lot
6 more detail.

7 You also have -- well, I think we already talked
8 about, if I'm not mistaken, the ESI protocol issue. I will
9 have to get with the magistrate on that, but that will be
10 something that we'll want to tee up early.

11 **MR. COFFIN:** Very early. Yes, Your Honor.

12 **THE COURT:** The defense, did you all have any
13 thoughts on that you wanted to comment on what was said?

14 **MR. STRONGMAN:** Nothing specific. We can certainly
15 work on a protocol. Once we know who we're negotiating with,
16 we'll go down that road.

17 **THE COURT:** Okay. No. 10 on your list, I think we
18 talked about the fact sheet issue, unless anyone has anything
19 to add.

20 The potential for a tolling agreement. Anybody
21 want to comment on that?

22 **MR. COFFIN:** Well, we have discussed this in earlier
23 cases earlier this year. We haven't come to an agreement, but
24 my understanding the last time we talked about it was that it's
25 potentially still on the table.

EXHIBIT C

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL)	:	
PRODUCTS LIABILITY LITIGATION	:	MDL NO. 2740
	:	
	:	SECTION "H" (5)
	:	
THIS DOCUMENT RELATES TO ALL	:	HON. JANE TRICHE MILAZZO
CASES	:	
	:	

**THIRD AMENDED MASTER LONG FORM COMPLAINT
AND DEMAND FOR JURY TRIAL
(PARTIALLY REDACTED)**

1. COME NOW, Plaintiffs, through the Plaintiffs' Steering Committee, who submit this Third Amended Master Long Form Complaint and Demand for Jury Trial ("Third Amended Master Complaint"). This Third Amended Master Complaint sets forth common allegations of Plaintiffs who were injured as a result of their exposure to brand-name drug products Taxotere, Docefrez, Docetaxel Injection Concentrate, and Docetaxel Injection that were approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FDCA"). These brand-name drug sponsors, manufacturers, labelers, and distributors are Defendants Sanofi S.A., Aventis Pharma S.A., Sanofi US Services Inc., Sanofi-Aventis U.S. LLC, Sandoz Inc., Accord Healthcare, Inc., McKesson Corporation d/b/a McKesson Packaging ("McKesson"), Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc., Hospira, Inc., Sun Pharma Global FZE, Sun Pharmaceutical Industries, Inc. f/k/a Caraco Pharmaceutical Laboratories Ltd., Pfizer Inc., Actavis LLC f/k/a Actavis Inc., Actavis Pharma, Inc., and Sagent Pharmaceuticals, Inc. (collectively "Defendants") for damages and such other relief deemed just and proper.

2. This Third Amended Master Complaint is intended to achieve efficiency and economy by presenting certain common allegations and common questions of fact and law that generally pertain

to Plaintiffs adopting this Complaint. Plaintiffs plead all Counts of this Third Amended Master Complaint and Jury Demand in the broadest sense, pursuant to all applicable laws and pursuant to choice of law principles, including the law of the each Plaintiff's home state.

3. This Third Amended Master Complaint does not necessarily include all claims asserted in all the transferred actions to this Court. It is anticipated that individual Plaintiffs will adopt this Third Amended Master Complaint and selected causes of action herein through the use of a separate Short Form Complaint. Any individual facts, jurisdictional allegations, additional legal claims and/or requests for relief of individual Plaintiffs may be set forth as necessary in the Short Form Complaint filed by the respective Plaintiffs. This Third Amended Master Complaint does not constitute a waiver or dismissal of any claims asserted in those individual actions, and no Plaintiff relinquishes the right to amend his or her individual claims to include additional claims as discovery and trials proceed.

INTRODUCTION

4. Taxotere is a chemotherapy drug administered to many who suffer primarily from breast cancer. Brand-name drug sponsors, manufacturers, labelers, and distributors of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, have known for years that these drugs cause permanent hair loss by preventing the regrowth of hair, a now well-documented side effect that for years has been publicized in numerous scientific studies, articles, and presentations. Despite this, these brand- name entities failed to warn patients and healthcare providers of the risk of permanent hair loss and report this risk to the Food and Drug Administration ("FDA"). Instead, Defendants hid this devastating side effect.

5. Plaintiffs are women who were diagnosed with breast cancer, underwent chemotherapy using Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and/or Docefrez, and now suffer from permanent hair loss, a side effect for which they were not warned and were wholly unprepared. Had Plaintiffs and Plaintiffs' healthcare providers known that permanent

hair loss could result, they would have selected a different treatment option—effective alternatives to these drugs that do not lead to this devastating side effect are used regularly.

6. As a result of this undisclosed side effect, Plaintiffs have struggled to return to normalcy, even after surviving cancer because an integral element of their identities, their hair, never returned. Plaintiffs are stigmatized with the universal cancer signifier—baldness—long after they underwent cancer treatment, and their hair loss acts as a permanent reminder that they are cancer victims. This permanent change has altered Plaintiffs’ self-image, negatively impacted their relationships, and others’ perceptions of them, leading to social isolation and depression even long after fighting cancer.

7. Defendants failed, and some still fail, to adequately warn that permanent or irreversible hair loss is a common side effect of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, and Plaintiffs have been unable to weigh this devastating possibility when deciding among treatment options. Plaintiffs seek recovery for their mental and physical suffering stemming from permanent or irreversible hair loss.

THE PARTIES

A. Plaintiffs

8. This Third Amended Master Complaint is filed on behalf of all Individual Injured Plaintiffs (“Plaintiffs”) whose claims are subsumed within MDL No. 2740. Plaintiffs in these individual actions have suffered personal injuries as a result of the use of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez. In addition, and where applicable, this Third Amended Master Complaint is also filed on behalf of Plaintiffs’ spouses, children, parents, decedents, wards and/or heirs, all represented by Plaintiffs’ counsel.

9. Plaintiffs have suffered personal injuries as a direct and proximate result of Defendants’ conduct and misconduct as described herein and in connection with the design,

development, manufacture, testing, packaging, promotion, advertising, marketing, distribution, labeling, warning, and sale of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez.

10. Plaintiffs could not, by the exercise of reasonable diligence, have discovered that their usage of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez resulted in their injuries. In fact, Defendants have yet to acknowledge that these drugs permanently prevent hair regrowth, and Plaintiffs did not suspect, nor did they have reason to suspect that these drugs prevented hair regrowth or the tortious nature of the conduct causing their injuries until a date prior to the filing of these actions, which is less than the applicable limitations period for filing suit.

11. Additionally, Plaintiffs were prevented from discovering this information at an earlier date because: (1) Defendants misrepresented to the public and the medical profession that Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, are free from permanent side effects; (2) Defendants failed to disclose to the public and the medical profession their knowledge of the risk that these drugs could permanently prevent hair regrowth; and (3) Defendants fraudulently concealed facts and information that could have led Plaintiffs to discover the liability of the Defendants.

B. Sanofi-Related Entities

12. Defendant Sanofi S.A. f/k/a Sanofi Aventis S.A. is the owner and operator of a multinational vertically integrated pharmaceutical company organized and existing under the laws of France with a principal place of business at 54 Rue La Boétie, 75008 Paris, France. Sanofi S.A. formed in 2004 after Sanofi-Synthelabo acquired Aventis Group, including subsidiary Defendant Aventis Pharma, S.A. Sanofi S.A. is engaged in research and development, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing of prescription drugs, including Taxotere. American Depositary Receipts for Sanofi SA are traded on the New York Stock Exchange.

It is the only publicly traded company among the various Sanofi entities named as defendants in the case.

13. Defendant Aventis Pharma S.A. is a corporation organized and existing under the laws of France with a principal place of business at 20 Avenue Raymond Aron, 92160 Antony, France. Aventis Pharma S.A. is a wholly owned subsidiary of Defendant Sanofi S.A. Defendant Aventis Pharma S.A. is the owner/holder of the patents for Taxotere. Aventis Pharma S.A. previously sought to protect Taxotere patents by filing an action for patent infringement in the United States District Court for the District of Delaware and availing itself of United States law.

14. Upon information and belief, at the direction of Sanofi S.A., Defendant Aventis Pharma S.A. licensed the patents for Taxotere to Defendants Sanofi US Services Inc. and Sanofi-Aventis U.S. LLC.

15. Defendant Sanofi US Services Inc. f/k/a Sanofi-Aventis U.S. Inc. is a Delaware corporation, with a principal place of business at 55 Corporate Drive, Bridgewater, New Jersey 08807. Sanofi US Services Inc. is a wholly owned subsidiary of Defendant Sanofi S.A. Defendant Sanofi US Services Inc. engages in research and development, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing of prescription drugs, including Taxotere.

16. Defendant Sanofi-Aventis U.S. LLC is a Delaware limited liability company, with a principal place of business at 55 Corporate Drive, Bridgewater, New Jersey 08807. Sanofi-Aventis U.S. LLC is a wholly owned subsidiary of Defendant Sanofi S.A., and Sanofi S.A. is Sanofi-Aventis U.S., LLC's sole member. Defendant Sanofi-Aventis U.S. LLC engages in research and development, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing of prescription drugs, including Taxotere.

17. Defendant Sanofi-Aventis U.S. LLC d/b/a Winthrop U.S. operates, promotes, markets, sells, distributes generic pharmaceutical products under the name of Winthrop U.S., which is a

business unit and/or division operating within and part of Sanofi-Aventis U.S. LLC.

18. Since 2006, Defendants Sanofi-Aventis U.S. LLC and Sanofi US Services Inc. have collectively served as the U.S. operational front for Defendant Sanofi S.A. in the U.S. prescription drug market. Prior to 2006, Aventis Pharmaceuticals Inc. served as the U.S. operational front for Defendant Sanofi S.A. in the U.S. prescription drug market until Aventis Pharmaceuticals Inc. merged with Sanofi S.A.

19. Defendant Sanofi S.A. is the alter ego of wholly owned subsidiary Defendants Aventis Pharma S.A., Sanofi US Services Inc., and Sanofi-Aventis U.S. LLC; Defendant Sanofi S.A. is using these named subsidiary Defendants as its agents; and/or Defendant Sanofi S.A. and the named subsidiary Defendants are one single integrated enterprise.

20. Defendant Sanofi S.A.’s Executive Vice-President of Pharmaceutical Operations in 2004, Hanspeter Spek, publicly stated in Sanofi S.A.’s Annual Report that the company was committed to growing its international presence by focusing on the United States, noting that “no pharmaceutical firm can call itself international unless it has achieved success and made its mark [in the United States].”

21. According to Mr. Spek, Defendant Sanofi S.A. was well-suited to handle the complexities of the U.S. pharmaceutical market, explaining:

When you look at current trends in the U.S., you see a form of regionalization between different states beginning to emerge. That’s a sign that the U.S. market is also becoming more complex in response to the country’s economic constraints, pressure on prices, and so on. These are factors that we know and are used to dealing with; we have the experience and the knowhow to cope with them in all serenity.

22. In fact, Defendant Sanofi S.A. has provided the financial resources and human capital, installing “a management team made up of a perfect mix of U.S. and European talents” and controlling the operations of subsidiary Defendants Aventis Pharma S.A., Sanofi-Aventis U.S. LLC and Sanofi US Services Inc. by providing financing, Sanofi S.A.’s unique manufacturing “know-how,” direction

of sales force, and management of operational risks to subsidiary Defendants Aventis Pharma S.A., Sanofi-Aventis U.S. LLC and Sanofi US Services Inc.

23. Defendant Sanofi S.A. represents itself as a global company with over 110,000 employees in more than 100 countries, including approximately 17,000 employees in the United States. Sanofi S.A. touts a global sales force of tens of thousands of representatives, noting that these sales representatives, including those in the United States, “embody the [Sanofi] Group’s values on a day-to-day basis.”

24. In addition, Defendant Sanofi S.A. manages the cash surpluses of subsidiary Defendants Aventis Pharma S.A., Sanofi-Aventis U.S. LLC and Sanofi US Services Inc., including controlling and transferring equity holdings among Sanofi S.A.’s subsidiaries. Sanofi S.A. includes the earnings of its subsidiaries in its annual reports, noting that 36.2% of its annual sales come from the United States.

25. Sanofi S.A. also represents that it has 17 manufacturing sites, 2 development centers, and 8 distribution hubs in the United States, located in Florida, Georgia, Maryland, Massachusetts, Missouri, Nevada, New Jersey, Pennsylvania, Puerto Rico, Tennessee, Washington, and Washington, D.C.

26. Furthermore, Defendant Sanofi S.A. formulates and coordinates the global strategy for Sanofi business and maintains central corporate policies regarding Sanofi subsidiaries, including subsidiary Defendants named herein, under the general guidance of the Sanofi group control. For example, Sanofi S.A. has a corporate tax policy overseen by Sanofi S.A.’s Tax Department.

27. Employees of Sanofi S.A. and its subsidiaries maintain reporting relationships that are not defined by legal, corporate relationships, but in fact cross corporate lines. For example, the U.S. heads of Human Resources, Communications, and Public Affairs are not affiliated with any specific U.S. subsidiary but serve as heads of Sanofi’s North American organizations, overseeing strategies

and activities for the entire North American region. For Human Resources specifically, Defendant Sanofi S.A. has adopted the “One Sanofi, One HR” concept to harmonize and align human resources practices across of Sanofi S.A.’s business activities, blurring corporate lines. In 2013, Sanofi S.A. launched the Short Term Work Assignment Program (“SWAP”), an employee exchange program that features six-month job exchanges between Sanofi employees in mature and emerging markets.

28. Defendant Sanofi S.A. has a number of policies for employee benefits and salaries that cross corporate lines. In 2001, Sanofi launched the “essential protection” project. This project provided all employees, across corporate lines, with coverage against unexpected events: illness, death benefit, and short and long term disability. This project also provided for compulsory pensions for all employees. Sanofi S.A. also has a compensation policy that all Sanofi subsidiaries have to follow. This policy aims to offer all employees in all subsidiaries compensation that is superior to the average salary for the pharmaceutical market. Each subsidiary’s employee benefits and salary program is subject to a preliminary approval procedure by Sanofi S.A. This means that Sanofi S.A. dictates the salary levels and benefits that must be paid to employees of its subsidiaries. Defendant Sanofi S.A. also controls research and development activities for Defendants Sanofi- Aventis U.S. LLC and Sanofi US Services Inc. by defining priorities, coordinating work, and obtaining the industrial property rights under Sanofi S.A.’s name and at Sanofi S.A.’s own expense. As mentioned above, Sanofi has a global Research & Development organization that works closely with Sanofi’s Senior Leadership Team.

29. On November 6, 2015, Sanofi S.A. CEO Oliver Brandicourt presented a “strategic roadmap,” a plan to restructure the company and simplify the organizational structure. Before the restructuring, Research & Development, Industrial Affairs, Finance, Human Resources, Business Development & Strategy, External Affairs, Information Systems, Medical, Legal, Compliance, & Procurement were globalized functions. After the restructuring, Sanofi S.A. introduced plans to move further to a Global Business Unit organization and divide its products into five globalized units:

Diabetes and Cardiovascular, General Medicines and Emerging Markets, Specialty Care, Vaccines, and Animal Health. The restructuring additionally included plans to reshape Sanofi’s global network of manufacturing plants. As a result of the restructuring Sanofi S.A. announced it would be cutting about 20 percent of its U.S. staff from its diabetes and cardiovascular unit alone with more U.S. staff cuts likely to come in the future.

30. Defendants Sanofi S.A. and Aventis Pharma S.A., through Sanofi-Aventis U.S. LLC and Sanofi US Services Inc., marketed Taxotere throughout the United States by providing marketing information regarding Taxotere to health care providers and similarly soliciting purchases for the drug.

31. Defendants Sanofi S.A. and Aventis Pharma S.A. expected that Taxotere would be sold, purchased, and used throughout the United States. In fact, Defendants Sanofi S.A. and Aventis Pharma S.A., through Sanofi-Aventis U.S. LLC and Sanofi US Services Inc., distributed and sold Taxotere to healthcare providers and patients throughout the United States.

C. Other Brand Name Drug Sponsors, Manufacturers, Labelers, and Distributors

32. In addition to the Sanofi-related entities, other brand-name entities obtained approval to market new drugs with the proprietary names Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate. Their new drug applications were approved under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (“FDCA”), codified at 21 U.S.C. § 355(b)(2).

33. A 505(b)(2) application is a subset of NDA, and it is subject to the NDA approval requirements set out in section 505(b) and (c) of the FDCA. As such, it must satisfy the requirements for safety and effectiveness information.

34. A 505(b)(2) application contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference.

35. Accordingly, a 505(b)(2) applicant may rely on the findings of safety and effectiveness of a listed drug to the extent the new product seeking approval and the listed drug are the same. Otherwise, to the extent the products are different, a 505(b)(2) application, like a 505(b)(1) application, must include sufficient data to demonstrate that the product with those different aspects meets the statutory approval standard for safety and effectiveness.

36. A drug approved under the 505(b)(2) approval pathway is not a generic copy of a brand-name drug. Section 505(b)(2) is not an appropriate approval pathway for an application for a duplicate drug eligible for approval under section 505(j) of the FDCA (the Abbreviated New Drug Application process).

1. Sandoz

37. Defendant Sandoz Inc. (“Sandoz”) is a pharmaceutical company organized and existing under the laws of the State of Colorado with a principal place of business at 100 College Road West, Princeton, New Jersey 08540.

38. Defendant Sandoz has transacted and conducted business throughout the United States.

39. Defendant Sandoz has derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

40. At all relevant times, Defendant Sandoz has been in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docetaxel Injection approved by the FDA under New Drug Application (“NDA”) #201525.

41. The proprietary name for Defendant Sandoz’s branded drug is Docetaxel Injection.

42. Defendant Sandoz expected that Docetaxel Injection would be sold, purchased, and used throughout the United States.

43. Defendant Sandoz filed NDA application #201525 on September 16, 2010, under Section 505(b)(2). Its application relied for its approval on FDA’s findings of safety and effectiveness

for the reference listed drug Taxotere.

44. Sandoz’s formulation of Docetaxel Injection, however, is different from Taxotere in that it contains less polysorbate 80 and more 96 percent ethanol. Also, it contains polyethylene glycol 300 as a solubizer and anhydrous citric acid for pH adjustment.

45. Sandoz received FDA approval for NDA #201525 on June 29, 2011 and began marketing the drug in the United States on August 15, 2011.

46. When the drug was approved, a portion of the Patient Counseling Information read as follows: “Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration.” It also stated that one of the “most common side effects of Docetaxel Injection” is “hair loss.” Neither of these statements refer to permanent hair loss.

47. Since approval, Sandoz has submitted multiple Changes Being Effectuated Supplemental New Drug Applications (“CBE sNDA”) to update labeling. It submitted a CBE sNDA (S-002) on July 29, 2011 that was approved on March 15, 2012, and a CBE sNDA (S-003) on August 15, 2013 that was approved on April 23, 2014. Neither submission, however, updated labeling concerning hair loss.

48. On October 21, 2016, the FDA approved Sandoz’s CBE sNDA, submitted on March 7, 2016, “to include information on permanent or irreversible alopecia to Section 6.2 (Post- marketing Experience), Section 17 (Patient Counseling Information) of the Package Insert, and the Patient Package Insert (PPI) labeling.”

49. As of December 2015, under “Post-Marketing Experiences,” the labeling states: “Cases of permanent alopecia have been reported.” Its Patient Counseling Information states that “side effects such as [...] hair loss (cases of permanent hair loss have been reported) are associated with docetaxel administration.” Its patient information also states that the “most common side effects” include “hair loss, in most cases normal hair growth should return. In some cases (frequency not known) permanent hair loss has been observed.”

50. There is no mention of the risk of permanent or irreversible hair loss, however, in the Warnings and Precautions or Adverse Reactions portions of its labeling.

2. Accord Healthcare & McKesson

51. Defendant Accord Healthcare, Inc. (“Accord”) is a pharmaceutical company organized and existing under the laws of the State of North Carolina with a principal place of business at 1009 Slater Road, Suite 210-B, Durham, North Carolina 27703.

52. Defendant McKesson Corporation d/b/a McKesson Packaging (“McKesson”) is a pharmaceutical company organized and existing under the laws of the State of Delaware with a principal place of business at One Post Street, San Francisco, California 94104.

53. Defendants Accord and McKesson have transacted and conducted business throughout the United States.

54. Defendants Accord and McKesson have derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

55. At all relevant times, Defendant Accord has been in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docetaxel Injection approved by the FDA under NDA #201195. Defendant Accord expected that Docetaxel Injection would be sold, purchased, and used throughout the United States.

56. At all relevant times, Defendant McKesson has been in the business of packaging and distributing Docetaxel Injection approved by the FDA under NDA #201195. Defendant McKesson expected that Docetaxel Injection would be sold, purchased, and used throughout the United States.

57. Defendant Accord filed NDA #201195 on December 7, 2010, under Section 505(b)(2). Its application relied for its approval on FDA’s findings of safety and effectiveness for the reference listed drug Taxotere.

58. Accord’s two-vial formulation, however, was different from Taxotere’s two-vial formulation in that it added new excipients citric acid (as a pH adjusting agent) and polyethylene glycol (PEG 400) (added to the diluent vial at 13 percent w/v). A one-vial formulation by Accord was later added in the same concentration and doses as the one-vial Taxotere, with the addition of a 160 mg / 8 mL “multiple dose” form.

59. Accord received FDA approval for NDA #201195 on June 8, 2011 and began marketing the drug in the United States on August 15, 2011.

60. When the drug was approved, a portion of the Patient Counseling Information read as follows: “Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration.” It also stated that one of the “most common side effects of Docetaxel Injection” is “hair loss.” Neither statement refers to permanent hair loss.

61. On November 14, 2013, Accord submitted a CBE sNDA (S-006) that was unrelated to hair loss. It was approved on July 3, 2014. Prior to that, Accord had also submitted a Manufacturing sNDA (S-004) that, upon information and belief, resulted in various labeling changes on or before April 5, 2013, which did not relate to hair loss.

62. Accord submitted a CBE sNDA (S-009) that was approved on July 26, 2016. As a result, the current label states that “[c]ases of permanent alopecia have been reported.” Patient Counseling Information directs: “Explain to patients that side effects such as [...] hair loss (cases of permanent hair loss have been reported) are associated with docetaxel administration.” The Patient Information section now reads, in part: “The most common side effects of Docetaxel Injection include [...] hair loss, in most cases normal hair growth should return. In some cases (frequency not known), permanent hair loss has been observed.”

63. There is no mention of the risk of permanent or irreversible hair loss, however, in the Warnings and Precautions or Adverse Reactions portions of its labeling.

3. *Hospira Entities*

64. Defendant Hospira, Inc. is a pharmaceutical company organized and existing under the laws of the State of Delaware with a principal place of business at 275 N. Field Drive, Lake Forest, Illinois 60045.

65. Defendant Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc. is a pharmaceutical company organized and existing under the laws of the State of Delaware with a principal place of business at 275 N. Field Drive, Lake Forest, Illinois 60045.

66. Defendants Hospira, Inc. and Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc. (collectively “Hospira”) have transacted and conducted business throughout the United States.

67. Hospira has derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

68. At all relevant times, Hospira has been in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docetaxel Injection approved by the FDA under NDA #022234. Hospira expected that Docetaxel Injection would be sold, purchased, and used throughout the United States.

69. Hospira filed NDA #022234 on July 11, 2007 under Section 505(b)(2). Its application relied for its approval on FDA’s findings of safety and effectiveness for the reference listed drug Taxotere.

70. Hospira’s formulation, however, is different from Taxotere’s formulation in several ways. First, upon the filing of its NDA in 2007, its pre-mixed, one-vial solution differed from Taxotere’s original two-vial formulation, which required initial dilution. (Taxotere’s one-vial, “ready-to-use” formulation was not FDA approved until 2010.) Second, it is packaged at a concentration of 10 mg / mL, which is one-fourth of the strength of two-vial Taxotere and one-half the strength of one-vial Taxotere. Third, Hospira’s 10 mg / mL formulation was marketed in a 160 mg vial, in

addition to 20 mg and 80 mg vials. Fourth, whereas Taxotere labels all its dosage forms as “single-use,” Hospira’s 80 mg and 160 mg formulations are marketed as “multi-use.” Fifth, unlike Taxotere, Hospira’s Docetaxel Injection contains both citric acid and polyethylene glycol 300.

71. Hospira received FDA approval for NDA #022234 on March 8, 2011 and began marketing the drug in the United States on March 17, 2011.

72. When the drug was approved, a portion of the Patient Counseling Information read as follows: “Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration.” It also stated that one of the “most common side effects of Docetaxel Injection” is “hair loss.” Neither of these statements refer to permanent hair loss.

73. On September 11, 2013, Hospira submitted a “Prior Approval” sNDA (S-003) adding certain indications consistent with Taxotere’s package insert at the time. Hospira also included in this sNDA new safety information concerning ethanol intoxication, which the FDA had requested Hospira add by letter of April 21, 2014. The FDA approved this sNDA on July 10, 2014. This update, the most recent revision, did not concern hair loss.

74. There is no mention of the risk of permanent or irreversible hair loss in its labeling.

4. Sun Pharma Entities

75. Defendant Sun Pharma Global FZE (“Sun Pharma Global”) is a pharmaceutical company organized and existing under the laws of the Emirate of Sharjah with a principal place of business at Executive Suite #43, Block &, SAIF Zone, P.O. Box 122304, Sharjah, United Arab Emirates.

76. Defendant Sun Pharmaceutical Industries, Inc. f/k/a Caraco Pharmaceutical Laboratories, Ltd. (“Sun Pharma”) is a pharmaceutical company organized and existing under the laws of New Jersey with a principal mailing address of 270 Prospect Plains Road Cranbury, NJ 08512 United States.

77. Defendants Sun Pharma Global has transacted and conducted business throughout the United States, on its own behalf and through its agent and distributor Defendant Sun Pharma

78. Defendants Sun Pharma Global and Sun Pharma have derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

79. At all relevant times, Defendants Sun Pharma Global and Sun Pharma have been in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docefrez, approved by the FDA under NDA #022534. Defendants Sun Pharma Global and Sun Pharma expected that Docefrez would be sold, purchased, and used throughout the United States.

80. Defendant Sun Pharma Global filed NDA #022534 on April 23, 2009 under Section 505(b)(2). Its application relied for its approval on FDA's findings of safety and effectiveness for the reference listed drug Taxotere.

81. Sun Pharma Global's two-vial docetaxel formulation, however, is different from Taxotere's two-vial formulation for several reasons. First, as opposed to Taxotere's active ingredient vial, which solution is viscous, Sun Pharma Global's active ingredient vial contains a powder. Second, and relatedly, Sun Pharma Global's polysorbate 80 is found in the diluent vial. Third, Sun Pharma Global's diluent vial contains a higher percentage of ethanol (35.4 percent) than Taxotere's (13 percent). Fourth, Sun Pharma Global's concentration is two times that of the two-vial Taxotere.

82. Sun Pharma Global received FDA approval for NDA #022534 on May 3, 2011 and began marketing the drug in the United States in May 2011.

83. When the drug was approved, a portion of the Patient Counseling Information read as follows: "Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration." It also stated that one of the "most common side effects of" the drug is "hair loss."

Neither of these statements refer to permanent hair loss.

84. Sun Pharma Global submitted, through its agent Sun Pharma, a CBE sNDA (S-002) to the FDA on July 28, 2011, for a label change that was approved on July 13, 2012. It also submitted a “Prior Approval” sNDA (S-004) for a label change through its agent Sun Pharma on May 22, 2014, which was approved on October 30, 2014. Neither change related to hair loss.

85. Sun Pharma Global and Sun Pharma ceased marketing Docefrez in November 2015, and at no time has the labeling for Docefrez referred to permanent or irreversible hair loss.

5. Pfizer

86. Defendant Pfizer Inc. (“Pfizer”) is a pharmaceutical company organized and existing under the laws of the State of Delaware with a principal place of business at 235 E 42nd Street, New York, NY 10017.

87. Defendant Pfizer has transacted and conducted business throughout the United States.

88. Defendant Pfizer has derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

89. At all relevant times, Pfizer has been in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docetaxel Injection approved by the FDA under NDA #202356. Pfizer expected that its Docetaxel Injection would be sold, purchased, and used throughout the United States.

90. Pfizer filed NDA #202356 on September 13, 2013, under Section 505(b)(2). Its application relied for its approval on FDA’s findings of safety and effectiveness for the reference listed drug Taxotere.

91. Pfizer’s one-vial formulation, however, was different from Taxotere’s one-vial formulation in that it added 130 mg / 13 mL and 200 mg / 20 mL dosage forms. Further, ethanol and propylene glycol were added as excipients in amounts greater than in Taxotere.

92. Pfizer received FDA approval for NDA #202356 on March 13, 2014 and began marketing the drug in the United States on June 23, 2014.

93. When the drug was approved, a portion of the Patient Counseling Information read as follows: “Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration.” It also stated that one of the “most common side effects of” the drug is “hair loss.” Neither of these statements refer to permanent hair loss.

94. Pfizer stopped marketing the 200 mg / 20 mL dosing of its Docetaxel Injection on October 31, 2016. In addition, Pfizer stopped marketing the 20 mg / 2 mL dosing and the 80 mg / 8 L dosing of its Docetaxel Injection on December 31, 2016.

95. Upon information and belief, Pfizer continues to market that 130 mg / 13 mL dosing of its Docetaxel Injection.

96. There is no mention of the risk of permanent or irreversible hair loss in its labeling.

6. Actavis Entities

97. Defendant Actavis Inc., now known as Actavis LLC, is a pharmaceutical limited liability company organized and existing under the laws of the State of Delaware with a principal place of business at 60 Columbia Road, Building B, Morristown, New Jersey 07960 and 400 Interpace Parkway, Parsippany, New Jersey 07054.

98. Defendant Actavis Pharma Inc. is a pharmaceutical company organized and existing under the laws of the State of Delaware with a principal place of business at 400 Interpace Parkway, Parsippany, New Jersey 07054. In 2016, Teva Pharmaceutical Industries, Ltd. acquired Defendant Actavis Pharma Inc. Prior to 2016, Actavis Pharma Inc. was a wholly owned subsidiary of Defendant Actavis LLC f/k/a Actavis Inc.

99. Defendant Sagent Pharmaceuticals, Inc. (“Sagent”) is incorporated under the laws of Delaware and maintains a principal place of business at 1901 N. Roselle Road, Ste. 700, Schaumburg,

IL 60195.

100. Defendants Actavis LLC f/k/a Actavis Inc. and Actavis Pharma Inc. (collectively “Actavis”) and Sagent transacted and conducted business throughout the United States.

101. Actavis and Sagent derived substantial revenue from goods and products designed, manufactured, marketed, advertised, promoted, sold, and distributed throughout the United States.

102. At all relevant times, Actavis and Sagent was in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and/or distributing Docetaxel Injection Concentrate approved by the FDA under NDA #203551. Actavis and Sagent expected that Docetaxel Injection Concentrate would be sold, purchased, and used throughout the United States.

103. Actavis filed NDA #203551 on March 14, 2012 under Section 505(b)(2). Its application relied for its approval on FDA’s findings of safety and effectiveness for the reference listed drug Taxotere.

104. Actavis and Sagent’s one-vial formulation, however, was different from Taxotere’s one-vial formulation because it is offered at an additional 140 mg dosage form, contains excipients citric acid and Kollidor 12 PF (Povidone k12), and uses reduced levels of polysorbate 80. After Actavis’ initial docetaxel approval, a 160 mg dosage form was also introduced.

105. Actavis received FDA approval for NDA #203551 on April 12, 2013 and began marketing these dosage forms on July 1, 2013.

106. When the drug was approved, a portion of the Patient Counseling Information read as follows: “Explain to patients that side effects such as [...] hair loss are associated with docetaxel administration.” It also stated that one of the “most common side effects of” the drug is “hair loss.” Neither of these statements refer to permanent hair loss.

107. Actavis submitted a CBE sNDA (S-001) on May 14, 2013, which was approved on November 4, 2013. Actavis also submitted a “Prior Approval” sNDA (S-002) on March 21, 2014,

which was approved on September 17, 2014. Neither resulting label change related to hair loss.

108. There is no mention of the risk of permanent or irreversible hair loss in its labeling.

JURISDICTION AND VENUE

109. Federal subject-matter jurisdiction in the constituent actions is based upon 28 U.S.C. § 1332(a). Plaintiffs allege the existence of subject-matter jurisdiction, and absent objection, there is complete diversity among Plaintiffs and Defendants and the amount in controversy exceeds \$75,000.

110. A substantial part of the events and omissions giving rise to Plaintiffs' causes of action occurred in the federal judicial district identified in the Short Form Complaint. Pursuant to 28 U.S.C. § 1391(a), venue is proper there.

111. Pursuant to the Transfer Orders of the Judicial Panel on Multidistrict Litigation, venue in actions sharing common questions with the initially transferred actions is proper in this district for coordinated pre-trial proceedings pursuant to 28 U.S.C. § 1407.

112. Defendants have significant contacts with the federal judicial district identified in the Short Form Complaint such that they are subject to the personal jurisdiction of the court in that district.

FACTUAL ALLEGATIONS

A. Development, Approval, and Labeling Changes for Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez

113. Taxotere is a drug used in the treatment of various forms of cancer, including breast cancer, and is a part of a family of cytotoxic drugs referred to as taxanes.

114. Taxanes are derived from yew trees, and unlike other cytotoxic drugs, taxanes inhibit the multiplication of cancer cells by over-stabilizing the structure of a cancer cell, which prevents the cell from breaking down and reorganizing for cell reproduction. They are widely used as chemotherapy agents.

115. The development of taxanes began in the 1960s. Bristol-Myers Squibb developed, manufactured, and distributed the first commercially available taxane in the United States, known as

Taxol (paclitaxel).

116. Taxol is the main competitor drug to Taxotere, and has been on the market since 1993.

117. Both docetaxel (Taxotere) and paclitaxel (Taxol) disrupt the microtubular network in cells that is essential for mitotic and interphase cellular function in the cell multiplication process.

118. Taxotere began as a two-vial product. One vial is called a concentrate, and it contains docetaxel, along with polysorbate 80 and residual amounts of ethanol. The other vial is a diluent, containing water and ethanol.

119. The concentrate vial and the diluent vial are combined to form a “premix.” A premix can be added to an intravenous bag to make a prefusion.

120. Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez are not purchased by patients at a pharmacy; rather, patients use of these drugs occurs via administration through injection and/or intravenously at a physician’s office or medical treatment facility.

121. In the 1980s scientists at Rhône-Poulenc Rorer S.A., Defendant Sanofi S.A.’s predecessor-in-interest, began developing Taxotere with the intention of making a more potent taxane. Since that time, Defendants Sanofi S.A., Aventis Pharma S.A., Sanofi US Services Inc., Sanofi-Aventis U.S. LLC, and their affiliates and predecessors-in-interest (collectively “Sanofi”) have controlled the development and been the owner, holder, or assignee of the patents related to Taxotere.

122. Phase I clinical testing of Taxotere began in 1990 (called the “TAX 001” study) and continued until 1992. Sanofi reported the results of clinical testing in May 1994.

123. Soon thereafter, on July 27, 1994, Sanofi applied for FDA approval for Taxotere under NDA #20449. The FDA’s Oncologic Drugs Advisory Committee panel unanimously denied approval of the drug, requesting more data on toxicity, side effects, and phase III test results.

124. After additional clinical testing, the FDA approved Taxotere in May 14, 1996 for limited use—namely, for the treatment of patients with locally advanced or metastatic breast cancer

that had either (1) progressed during anthracycline-based therapy or (2) relapsed during anthracycline-based adjuvant therapy.

125. The label approved for Taxotere for this indication reflected the medical community's understanding that temporary hair loss is commonly associated with chemotherapy drugs and provided no information about the risk of permanent alopecia.

126. In fact, the clinical trial sponsored by Sanofi to support initial approval did not evaluate alopecia as a long-term side-effect of Taxotere.

127. After the initial approval, Sanofi sought and received FDA approval for additional indications. Based on self-sponsored clinical trials, Sanofi claimed Taxotere's superiority over competing chemotherapy products approved for breast cancer treatment, including claiming superior efficacy over the lower potency paclitaxel (Taxol), its primary competitor.

128. On June 22, 1998, the FDA approved a slightly broader indication for Taxotere that extended its use to patients with locally advanced or metastatic breast cancer as treatment after "failure of prior chemotherapy."

129. That same year, Sanofi obtained FDA approval in December 1999 for use of Taxotere in treating "locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy."

130. As with all prior FDA-approved indications for Taxotere, the drug was approved at this time, and until late 2002, only as a second-line of treatment, meaning that Sanofi was prohibited from promoting Taxotere for use in patients who had not undergone and failed a specified first-line of treatment.

131. Sanofi obtained FDA approval in November 2002 for use of Taxotere "in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition."

132. Sanofi obtained FDA approval in May 2004 for use of Taxotere “in combination with prednisone as a treatment for patients with androgen independent (hormone refractory) metastatic prostate cancer.”

133. Also that year, Sanofi obtained FDA approval in August 2004 for use of Taxotere “in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.”

134. In March 2006, Sanofi obtained FDA approval for use of Taxotere “in combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.”

135. Sanofi obtained FDA approval in October 2006 for use of Taxotere “in combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN).” In September 2007, FDA approved a broader SCCHN indication that removed the condition of inoperability.

136. Sanofi obtained FDA approval in May 2010 to add language related to pediatric safety and efficacy, including: “The overall safety profile of TAXOTERE in pediatric patients receiving monotherapy or TCF was consistent with the known safety profile for adults.” Additional changes to this label included a number of edits described by Sanofi as “housekeeping” that, among other things, deleted the phrase “hair generally grows back” and added “most common side effects of TAXOTERE include: [...] hair loss” to the “Patient Information” section of the label. As with previous labels, the May 2010 label provides no information about irreversible or permanent hair loss.

137. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

138. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

139. [REDACTED]

[REDACTED]

[REDACTED]

140. [REDACTED]

[REDACTED]

[REDACTED] Sanofi then submitted a CBE sNDA on November 24, 2015 adding the language “cases of permanent alopecia have been reported” to the “Adverse Reactions” and “Patient Counseling Information” sections of the label. Sanofi also made changes to the “Patient Information” section of the label adding that the most common side effects of TAXOTERE include “hair loss: in most cases normal hair growth should return. In some cases (frequency not known) permanent hair loss has been observed.” The FDA approved Sanofi’s sNDA on December 11, 2015.

141. On April 11, 2018, Sanofi submitted a Prior Approval sNDA, request that the Taxotere label be updated to identify adverse events occurring at the conclusion of the follow-up period in TAX 316 in 2010. Among the adverse events identified by Sanofi included 29 patients who had alopecia ongoing at a median follow-up of 10-years. FDA approved Sanofi’s proposed label change on October 5, 2018.¹

B. Defendants’ Duties Under the FDCA and State Law

142. The primary responsibility for timely communicating complete, accurate and current

¹ https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2018/020449Orig1s079ltr.pdf

[REDACTED]

safety and efficacy information related to prescription drugs rests with NDA holders/drug sponsors (such as manufacturers or labelers) and their assigns or agents; they have superior, and in many cases exclusive, access to the relevant safety and efficacy information, including post- market complaints and data.

143. To fulfill their essential responsibilities, these entities must vigilantly monitor all reasonably available information. They must closely evaluate the post-market clinical experience of their drugs and timely provide updated safety and efficacy information to the healthcare community and to consumers.

144. When monitoring and reporting adverse events, as required by both federal regulations and state law, time is of the essence. The purpose of monitoring a product’s post- market experience is to detect potential safety signals that could indicate to drug sponsors and the medical community that a public safety problem exists. If, for example, a manufacturer were to delay in reporting post-market information, that delay could mean that researchers, FDA, and the medical community are years behind in identifying a public safety issue associated with the drug. In the meantime, more patients are harmed by using the product without knowing, understanding, and accepting its true risks. This is why drug sponsors must not only completely and accurately monitor, investigate and report post-market experiences, but they must also report the data in a timely fashion.

145. Because complete information about the safety of a drug cannot be known at the time of approval, and because the true picture of a product’s safety profile emerges over time because of use by patients, it is a central premise of federal drug regulation that the NDA holders and their assigns or agents—not the FDA—bear responsibility for the content of its label at all times. Consequently, NDA holders are primarily responsible for crafting an adequate label and ensuring that warnings remain adequate as long as the drug is on the market.

146. A drug is “misbranded” in violation of the FDCA when its labeling is false and

misleading, or does not provide adequate directions for use and adequate warnings. See 21 U.S.C. §§ 321(n); 331(a), (b), (k); 352(a), (f). A drug's labeling satisfies federal requirements if it gives physicians and pharmacists sufficient information—including indications for use and “any relevant hazards, contraindications, side effects, and precautions”—to allow those professionals “to use the drug safely and for the purposes for which it is intended.” 21 C.F.R. § 201.100(c)(1).

147. As part of their responsibility to monitor post-market clinical experiences with the drug and provide updated safety and efficacy information to the healthcare community and to consumers, each approved NDA applicant, whether under 505(b)(1) or (2), “must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, post marketing clinical investigations, post marketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.” 21 C.F.R. § 314.80(b). Any report of a “serious and unexpected” drug experience, whether foreign or domestic, must be reported to the FDA within 15 days and must be promptly investigated by the manufacturer. 21 C.F.R. § 314.80(c)(1)(i-ii). Most other adverse event reports must be submitted quarterly for three years after the application is approved and annually thereafter. 21 C.F.R. § 314.80(c)(2)(i). These periodic reports must include a “history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).” 21 C.F.R. § 314.80(c)(2)(ii).

148. Federal law requires labeling to be updated as information accumulates: “labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.” 21 C.F.R. § 201.57(c)(6)(i). Thus, for example, drug manufacturers must warn of an adverse effect where there is “some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.” 21 C.F.R. § 201.57(c)(7).

149. All changes to drug labeling require FDA assent. 21 C.F.R. § 314.70(b)(2)(v)(A). Brand-name drug sponsors, including those whose drugs were approved under Section 505(b)(2), may seek to change their approved labels by filing a supplemental application. 21 C.F.R. § 314.70.

150. One regulation, the “Changes Being Effected” (CBE) regulation, permits a manufacturer to unilaterally change a drug label to reflect “newly acquired information,” subject to later FDA review and approval. 21 C.F.R. § 314.70(c)(6)(iii). Newly acquired information includes “new analyses of previously submitted data.” 21 C.F.R. § 314.3(b). Thus, for instance, if a drug sponsor were to determine that a warning were insufficient based on a new analysis of previously existing data, it could submit a CBE and change its labeling.

151. The longer a drug sponsor delays updating its labeling so that it reflects current safety information, the more likely it is that medical professionals will continue to prescribe drugs without advising patients of harmful side effects, and the more likely it is that patients will suffer harmful side effects without the opportunity to evaluate risks for themselves.

C. Defendants Knew that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate May Cause Permanent Alopecia.

152. In 1997, Sanofi initiated TAX 316, a self-sponsored clinical trial comparing the effects of a regimen of fluorouracil, doxorubicin, and cyclophosphamide (“FAC”) with a regimen of docetaxel, doxorubicin, and cyclophosphamide (“TAC”) in patients with operable node-positive breast cancer. A total of 1040 patients from 112 centers participated in TAX 316 with 744 patients receiving TAC and 736 receiving FAC. In 2004, an interim analysis of TAX 316’s 55-month median follow-up data demonstrated that 3.2% of patients who took Taxotere had persistent alopecia.

153. Beginning in 1998, Sanofi sponsored a trial entitled GEICAM 9805. It was initiated to compare the effects of a regimen of fluorouracil, doxorubicin, and cyclophosphamide (“FAC”) with a regimen of docetaxel, doxorubicin, and cyclophosphamide (“TAC”) in patients with high- risk, node-negative breast cancer. Between June 1999 and March 2003, a total of 1060 patients from 55

centers were randomly assigned to receive either TAC or FAC. By 2005, it knew that the GEICAM 9805 study demonstrated that 9.2 percent of patients who took Taxotere had persistent alopecia.

154. In March 2006, Sanofi’s pharmacovigilance department received an inquiry from a physician about the reversibility of alopecia following Taxotere treatment, noting that a patient had been experiencing alopecia since 2004. In response, Sanofi’s Global Safety Officer for Taxotere internally acknowledged that cases of irreversible alopecia had occurred during Sanofi’s clinical trials for Taxotere and that the medical literature might contain additional reports of irreversible alopecia. Despite this, Sanofi’s Global Safety Officer advised against doing a literature search on the topic of irreversible alopecia and Taxotere. In addition, Sanofi withheld this information from the Taxotere label and concealed it from the medical community and consumers, including Plaintiffs.

155. In December 2006, an oncologist from Denver, Colorado, Dr. Scot Sedlacek, presented a study entitled “Persistent significant alopecia (PSA) from adjuvant docetaxel after doxorubicin/cyclophosphamide (AC) chemotherapy in women with breast cancer.” Dr. Sedlacek tracked patients in three groups: Group A (doxorubicin regimen without a taxane); Group B (doxorubicin plus paclitaxel) and Group C (doxorubicin plus docetaxel). No women in Group A or Group B experienced persistent significant alopecia, but 6.3 percent of those in Group C did. Dr. Sedlacek concluded “that when docetaxel is administered after 4 doses of AC, there is a small but significant possibility of poor hair regrowth lasting up to 7 years. Such an emotionally devastating long term toxicity from this combination must be taken into account when deciding on adjuvant chemotherapy programs in women who likely will be cured of their breast cancer.”

156. On November 21, 2008, Sanofi responded to an inquiry from a patient in the United Kingdom concerning Taxotere and the incidence of permanent alopecia. That letter acknowledged that “one reference of non-reversible alopecia” had been identified. Its letter cited a paper published in the journal of Clinical Oncology for the proposition that “clinical studies ... showed one case of

non-reversible alopecia at the end of the study.” The letter also cited another paper from the New England Journal of Medicine, which stated that “studies involving Taxotere in combination with doxorubicin and cyclophosphamide observed alopecia to be ongoing at the median follow-up time of 55 months in 3 percent of patients at the end of the chemotherapy.”

157. In 2009, the British Journal of Dermatology published an article entitled “Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer.” That article reported a case in which a 58-year-old woman “developed diffuse and irreversible alopecia 7-years ago, after being treated with six cycles of docetaxel ... every 3 weeks for a local occurrence.” She did not have alopecia before administration of the chemotherapy. The article concluded “the irreversibility can be attributed only to the cytotoxic effect of docetaxel.”

158. By early 2010, Sanofi had received reports from hundreds of women describing their permanent hair loss following treatment with Taxotere. Despite this fact, Sanofi withheld this information from the label and concealed it from the medical community and consumers, including Plaintiffs.

159. On March 5, 2010, The Globe and Mail, a Canadian newspaper, published an article entitled “Women who took chemo drug say they weren’t warned of permanent hair loss.” The article explained: “Women who took a drug to fight breast cancer say they were never warned of a side effect—permanent hair loss—that left them looking sick long after they were treated for the disease.” The article described this permanent hair loss as a “lasting side effect of the chemotherapy drug Taxotere, in combination with other drugs.” The article included sufferers from Montreal, Canada; Brittany, France; and Oklahoma who had been treated with Taxotere. The article explained that the “side effect of persistent alopecia is suffered by about 3 percent of patients who take Taxotere with other chemotherapy drugs, according to the manufacturer’s own studies,” but that a “different study suggests that the incidence of persistent alopecia could be as high as 6 percent.”

160. The Globe and Mail article also cited medical oncologist Dr. Hugues Bourgeois of Le Mans, France, “who presented research on 82 patients with persistent alopecia at the San Antonio Breast Cancer symposium this winter.” Dr. Bourgeois described the choice he gives his patients—twelve cycles of Taxol or four cycles of Taxotere, where the risk of hair loss is higher. According to Dr. Bourgeois, most choose Taxol, which Dr. Bourgeois said “works just as well on breast cancer.”

161. On March 6, 2010, CBS News published an article entitled “Sanofi’s Latest Challenge: Women Who Say Its Chemotherapy Left Them Permanently Bald.” The article described a group of women who called themselves “Taxotears” and encouraged women who have lost all their hair to report the adverse events to Sanofi and drug watchdog authorities. It also noted that “Taxotere’s official prescribing information ... makes no mention of permanent alopecia,” and that “small studies suggest that as many as 6.3 percent of patients lose all their hair forever.”

162. The CBS News article also mentioned that the Medicines and Healthcare products Regulatory Agency in the United Kingdom noted that “it was aware of one study in which 22 of 687 patients (about 3 percent) had persistent baldness after nearly five years.”

163. On May 10, 2010, an article by Ben Tallon, MBChB, and others entitled “Permanent chemotherapy-induced alopecia: Case report and review of the literature” was published online. That article described “a case of permanent hair loss following standard dose chemotherapy with docetaxel, carboplatin, and trastuzumab for the treatment of breast carcinoma.” There, the “lack of evidence for alopecia with trastuzumab, and the exposure to only a single infusion of standard dose carboplatin, suggests that docetaxel is the implicated agent.” The article also explained: “Permanent [chemotherapy-induced alopecia] has been described following the use of ... docetaxel.”

164. Later in 2010, Sanofi completed its analysis of the ten-year follow-up results for TAX 316, the clinical trial used to support the adjuvant breast cancer indication. This analysis found that the number of women reporting persisting hair loss had increased from the 22 patients reported in

2004 to 29 patients out of the 687 patients tracked into follow-up. This represented an increase in the incidence of persistent alopecia from approximately 3% to 4.2%. Sanofi had previously decided in 2009 not to update the U.S. label with the follow-up data from TAX 316. Instead, Sanofi submitted to the FDA only the Final Clinical Study Report for TAX 316, which is over a thousand pages long, without submitting a labeling change. In addition, Sanofi continued to conceal this information from the medical community and consumers, including Plaintiffs.

165. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

166. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

167. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Instead, Sanofi

continued to conceal this information from the medical community and consumers in the United States, including Plaintiffs.

168. Also in 2011, the American Journal of Dermatopathology published a study entitled “Permanent Alopecia After Systemic Chemotherapy: A Clinicopathological Study of 10 Cases,” by Mariya Miteva, MD and others. The article discussed “the histological features of 10 cases of

permanent alopecia after systematic chemotherapy with taxanes (docetaxel),” including 6 cases in which the patients took docetaxel for breast cancer. “All patients had moderate to very severe hair thinning ...”

169. On May 9, 2012, the Annals of Oncology published an article entitled “Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/ epirubicin/ cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients,” by Nicolas Kluger, M.D.,Ph.D., among others. It reported that, since 2009, “nine cases of permanent scalp alopecia after systemic chemotherapy related to taxanes used to treat breast cancer have been reported ... Docetaxel was almost always involved, alone in seven cases ... or in association with carboplatin ... and trastuzumab.”

170. In October 2013, Drs. Nicola Thorp, Felicity Swift, Donna Arundell and Helen Wong presented at Clatterbridge Cancer Centre in the United Kingdom on “Long Term Hair Loss in Patients with Early Breast Cancer Receiving Docetaxel Chemotherapy.” Their study was based on a questionnaire sent in October 2013 to patients who received docetaxel in 2010. Out of 189 questionnaires, 134 were returned. “Of those responding 21 (15.8 percent) had significant persistent scalp hair loss.” The presentation concluded: “Long term significant scalp alopecia (hair lasting for up to 3.5 years following completion of chemotherapy) may affect 10-15 percent of patients following docetaxel for EBC. This appears to be unrelated to other patient and treatment characteristics ... This risk should be discussed routinely (as part of the process of informed consent) with all patients embarking upon docetaxel as a component of management of EBC.”

171. This Clatterbridge study was also published at the 2014 San Antonio Breast Cancer Symposium.

172. On November 10, 2015, the Journal of Clinical Oncology published an article entitled “Epirubicin Plus Cyclophosphamide Followed by Docetaxel Versus Epirubicin Plus Docetaxel

Followed by Capecitabine As Adjuvant Therapy for Node-Positive Early Breast Cancer: Results From the GEICAM/2003-10 Study.” This article reviewed and reiterated the connection between docetaxel and long-term alopecia:

Patients who received [docetaxel] not only had to wear a wig for a longer period of time but also reported a significantly higher proportion of long-term incomplete scalp hair recovery and permanent wig use after therapy. This adverse effect, probably related to docetaxel ... has previously been described by others. Sedlacek reported that approximately 6% of patients who received adjuvant docetaxel for early BC had persistent alopecia, whereas this toxicity was not seen in 384 patients receiving nondocetaxel adjuvant regimens. Kluger et al reported 20 patients with BC with persistent hair loss of androgenetic-like pattern after adjuvant treatment with CEF followed by docetaxel. Consequently, a prospective study of the efficacy of scalp hypothermia in the prevention of docetaxel-induced persistent alopecia is ongoing at one of the centers participating in the present trial.

173. Despite this, hair loss was listed as a “possible side effect[] of Taxotere” that “generally grows back” in a Patient Information Letter circulated by Sanofi beginning in December 23, 1999 and an informational brochure given to oncology nurses in 2006.

174. By contrast, the labeling for Taxotere approved by the European Medicines Agency in 2005 acknowledged that “[c]ases of persisting alopecia have been reported.” It also stated in a tabulated list of adverse reactions in breast cancer that took into account node-positive breast cancer (from TAX 316) and node-negative breast cancer (from GEICAM 9805) that alopecia is a “[v]ery common adverse reaction,” with persisting alopecia occurring under three percent of the time.

175. Likewise, in a self-sponsored clinical trial, the informed consent form provided by Sanofi to Canadian patients disclosed irreversible alopecia as a possible side effect but a similar informed consent form provided to United States patients in 2006 and 2007 did not. Again, Sanofi concealed this information from patients in the United States.

176. In the September 28, 2007 version of the Highlights of Prescribing Information in the United States, alopecia is listed as one of the most common adverse reactions. There is no mention of permanent alopecia.

177. The April 2010 version of Taxotere’s United States labeling stated that “hair generally grows back.” That language does not appear in the May 2010 version of Taxotere’s label. Instead, the 2011 version of the prescribing information stated under “Patient Counseling Information” that “side effects such as ... hair loss are associated with docetaxel administration.” “Patient Information” indicated that the “most common side effects of TAXOTERE include: ... hair loss.” The document contains no mention of irreversible or permanent hair loss. Instead, it states that “alopecia” is one of the most common adverse reactions. The November 2014 version of this labeling information contains the same text.

178. In May 2015, Sanofi UK updated its Taxotere label. That version states that a “[v]ery common” side effect is “hair loss (in most cases normal hair growth should return).”

179. On June 12, 2015, Canada’s Taxotere labeling changed. Its new labeling stated: “Hair loss may happen shortly after treatment has begun. Your hair should grow back once you’ve finished the treatment. However, some patients may experience persistent hair loss.

180. In August 2015, Australia’s Taxotere labeling changed. Its new labeling stated that alopecia was “observed to be ongoing at the median follow-up time of 55 months.”

181. In the United States, Sanofi submitted a CBE on November 24, 2015 concerning permanent alopecia.

182. On December 11, 2015, FDA approved the CBE. Under the “Adverse Reactions” and “Patient Counseling Information” sections of the label, Sanofi added the language that “cases of permanent hair loss have been reported.” In the “Patient Information” section, Sanofi added that the most common side effects of TAXOTERE include “hair loss: in most cases normal hair growth should return. In some cases (frequency not known) permanent hair loss has been observed.”

183. On April 11, 2018, Sanofi submitted a Prior Approval sNDA, request that the Taxotere label be updated to identify adverse events occurring at the conclusion of the follow-up period in TAX

316 in 2010. Among the adverse events identified by Sanofi included alopecia still ongoing at median follow-up of 8-years. FDA approved Sanofi's proposed label change on October 5, 2018.

184. Upon information and belief, Defendants failed to comply with the FDA postmarketing reporting requirements under 21 C.F.R. § 314.80 by, among other things, failing to report each adverse drug experience concerning the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate products, whether foreign or domestic, including Plaintiffs' injuries complained of herein, as soon as possible but in no case later than 15 calendar days after initial receipt of the information by Defendants, failing to promptly investigate all adverse drug experiences concerning these drug products that are the subject of these postmarketing 15-day Alert reports, failing to submit follow up reports within 15 calendar days of receipt of new information or as requested by the FDA, and, if additional information is not obtainable, failing to maintain records of the unsuccessful steps taken to seek additional information.

185. Also, consistent with the Changes Being Effected regulations, Defendants had and continue to have a duty to initiate a change to the products' labels to reflect the true levels of risk, including the risk of developing Plaintiffs' injuries complained of herein. To this day, Defendants have not adequately satisfied their duty to update the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate products' labeling or prescribing information to reflect their knowledge as to the true risks of developing the injuries complained of herein.

D. Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate Caused Permanent Alopecia in Many Breast Cancer Patients.

186. Chemotherapy is known to cause temporary and reversible hair loss. Hair loss occurs because chemotherapy targets rapidly dividing cells (both normal, healthy cells as well as cancer cells) including hair follicles. Hair follicles, the structures in the skin filled with tiny blood vessels that make hair, are some of the fastest growing cells in the body, thus, hair follicles are some of the most likely cells to be damaged by chemotherapy.

187. There are 100,000 hair follicles on the scalp that typically grow about 0.3 to 0.4 mm a day or about six inches a year. For hair production, hair follicles undergo a cycle that consists of three phases: the anagen phase (growth), the catagen phase (transition), and the telogen phase (resting). During the anagen phase, the cells at the root of the hair follicle are dividing rapidly and an entire hair shaft from tip to root is formed. The matrix cells, which build the hair shaft, have a cell cycle length of approximately 18 hours. Approximately 90 percent of the hair on the scalp is normally in the anagen phase.

188. The catagen phase is a short transitional phase that occurs at the end of the anagen phase when growth of a hair stops. Only about 3 percent of hair follicles are in the catagen phase at any time.

189. The hair follicle is completely at rest during the telogen phase and, at the end of the telogen phase, the hair falls out and a new hair is supposed to start growing in the hair follicle beginning the hair cycle again with the anagen phase. Around 6 to 8 percent of all hair is regularly in the telogen phase.

190. Chemotherapy causes the matrix cells to stop dividing abruptly in the anagen phase. As a result, the portion of the hair shaft that is the closest to the skull narrows and subsequently breaks within the hair canal. For this reason, hair loss usually begins one to three weeks after the initiation of chemotherapy and hair may fall out very quickly in clumps or gradually.

191. Because the majority of hair on the scalp is in the anagen phase during any given period, the hair loss that results from chemotherapy can be quite significant and visible.

192. The effects of chemotherapy on hair follicles results in temporary hair loss that lasts until the telogen phase is complete and a new hair cycle begins. According to the Mayo Clinic, hair can be expected to grow back after chemotherapy within three to six months. Dr. Ralph M. Trueb, the author of several articles related hair loss associated with chemotherapy, also states that hair regrowth

following chemotherapy treatment will occur within three to six months after cessation of treatment.

193. Unlike the temporary and reversible alopecia that ordinarily results from chemotherapy, Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate cause Permanent Chemotherapy Induced Alopecia.

194. There is no single definition for Permanent Chemotherapy Induced Alopecia and the amount of time to establish permanent hair loss varies from patient to patient, including among Plaintiffs. The scientific literature has variously referred to Permanent Chemotherapy Induced Alopecia as occurring between twelve to twenty-four months following chemotherapy treatment. Some literature has indicated that hair loss can be deemed “persistent” six months beyond the completion of chemotherapy.

195. Sanofi has stated in court filings that “persistent” alopecia generally describes hair loss for some duration of time following chemotherapy (e.g., 3 days, 30 days, 3 months, 6 months, etc.) and carries with it the potential for hair regrowth to occur.

196. Sanofi has also stated in court filings that “irreversible” or “permanent” alopecia, at a basic level means that an individual’s hair will never regrow.

197. Before this litigation and after, Sanofi has described Permanent Chemotherapy Induced Alopecia in a number of different ways. Employees of Sanofi have testified that permanent hair loss does not necessarily mean hair loss of six months. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

198. Upon information and belief, the varying definitions of Permanent Chemotherapy Induced Alopecia, as described above, were not reasonably knowable to prescribers or consumers of Taxotere, including Plaintiffs.

199. The Permanent Chemotherapy Induced Alopecia caused by Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate is not limited to the scalp and can affect hair follicles throughout the body.

200. Patients who receive Taxotere without any other type of chemotherapy have experienced permanent hair loss all over their bodies. For example, one oncologist reported he was unlikely to prescribe Taxotere in early stage breast cancer patients because of the toxicity of the drug. When prescribing Taxotere in early stage breast cancer cases, he recommended lower dosage levels over a longer period of time. His patients who have received Taxotere have experienced permanent hair loss.

201. Also, the GEICAM 9805, a study sponsored by Sanofi produced evidence that over 9 percent of high risk breast cancer patients who were administered Taxotere suffered permanent alopecia with hair loss lasting, in some cases, over ten years.

202. Dr. Sedlacek's 2006 study, as described above, further demonstrates that Taxotere causes permanent hair loss. His study divided patients he treated from January of 1994 to December of 2004 into three groups. The first group, which contained 258 patients, received Doxorubicin. None suffered permanent alopecia. The second group, which contained 126 patients, received Doxorubicin and Taxol. Again, none suffered permanent alopecia. The third group contained 112 patients who received Doxorubicin and Taxotere. Of those patients, 6.3 percent suffered permanent alopecia with hair regrowth of less than 50 percent of the amount before chemotherapy.

203. In addition, and as detailed above, Dr. Tallon's 2010 article concluded that, when a

cocktail of Taxotere, Trastuzumab, and Carboplatin was administered and there was resulting permanent alopecia, Taxotere was the implicated agent. Its reasoning was that there was a lack of evidence linking alopecia with Trastuzumab and limited exposure to Carboplatin. Trastuzumab does not contain a component that causes hair loss and does not increase the rate of hair loss when combined with standard chemotherapy. Similarly, Carboplatin causes only mild temporary alopecia in 5 percent of users.

204. Likewise, the 2012 study by Dr. Kluger and others concluded that Taxanes were responsible for permanent scalp alopecia among patients who were administered a sequential regimen of FEC (fluorouracil, epirubicin, and cyclophosphamide) followed by docetaxel. They noted that no patients treated with only anthracycline regimens (and not docetaxel) suffered from permanent severe scalp alopecia.

205. Further, Drs. Thorp, Swift, Arundell and Wong in their 2014 presentation reported that 15.8 percent of Taxotere patients surveyed had significant persistent scalp hair loss for up to 3.5 years following completion of chemotherapy.

206. Finally, Sanofi's change to the Taxotere label in 2015 and 2018, described above, acknowledges that Taxotere causes permanent hair loss but fails to do so adequately. Moreover, some Defendants have chosen not to adopt Sanofi's revised labeling. Under the "Patient Counseling Information" of the revised label, the new text reads: "Explain to patients that side effects such as ... hair loss (cases of permanent hair loss have been reported) are associated with docetaxel administration." Additionally, under "Patient Information," the label states that the "most common side effects of TAXOTERE include: ... hair loss: in most cases normal hair growth should return. In some cases (frequency not known) permanent hair loss has been observed." The label contains no mention of irreversible or permanent hair loss under "Warnings and Precautions" or "Adverse Reactions."

207. By contrast, in a report issued on Taxotere on May 12, 2016, the European Medicines Agency (“EMA”) concluded that “[b]ased on review of the Sanofi global pharmacovigilance database, worldwide scientific literature, clinical studies, and biological plausibility, the cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.”

208. Because NDA holders and their assigns or agents are held to the knowledge of an expert in the field concerning the products they sell, Defendants cannot plead ignorance of the scientific information publicly available or otherwise available to them that would have supported a label change, including the studies and information discussed herein.

E. Sanofi Marketed & Promoted Taxotere Despite Knowing It Caused Permanent Alopecia

209. Sanofi, including its predecessors and affiliates, have designed, directed, and/or engaged in a marketing scheme to over promote Taxotere directly to consumers and for off-label uses not approved by the FDA. As a result, Sanofi has earned in excess of €7 billion in revenue on its sales of Taxotere in the United States:

Year	U.S. Sales as Reported by Sanofi S.A.
2000	€367,000,000
2001	€541,000,000
2002	€701,000,000
2003	€733,000,000
2004	Could not be located
2005	€695,000,000
2006	€708,000,000
2007	€691,000,000
2008	€737,000,000
2009	€827,000,000
2010	€786,000,000
2011	€243,000,000
2012	€53,000,000
2013	€42,000,000
2014	€8,000,000

2015	€-1,000,000
2016	€4,000,000
Total	€7,135,000,000

210. In or around 2000, Sanofi hired a marketing firm to conduct a study on the primary concerns of oncologists and breast cancer patients undergoing treatment. The results of the study revealed that breast cancer patients felt an innate need to stay ‘connected’ through various means.

211. As a result of the marketing study, Sanofi launched a new sales promotional campaign in 2000 known as “Connection Cards” in which gift packages were offered to breast cancer patients at their oncologist’s office. These gift packages initially included ten custom designed note cards and envelopes; a 30-minute prepaid long-distance calling card; a reference card with contact information for nationally recognized breast cancer organizations; a reference card with contact information with the company’s breast cancer support program; and most importantly, a brochure giving detailed information about Taxotere.

212. To maintain the effectiveness of the promotional campaign, Sanofi added coupons for wigs and vouchers for discounted taxi services to the gift packages provided to breast cancer patients. In 2002, Sanofi made available to U.S. patients approximately 60,000 “Connection Cards” through 150 sales representatives.

213. Sanofi claimed the promotional campaign to be a success, adding the campaign to its permanent rotation of promotional materials.

214. Sanofi also promoted Taxotere for the following breast cancer treatments, which at the time, were neither approved by the FDA nor supported by the available drug compendia: adjuvant breast cancer, neo-adjuvant breast cancer, weekly dose for metastatic breast cancer.

215. Sanofi directed its U.S. sales force to misrepresent the safety and effectiveness of the off-label use of Taxotere to expand the market for Taxotere in unapproved settings, such as a first-line of treatment or for early-stage breast cancer.

216. On July 26, 2001, the FDA’s Division of Drug Marketing, Advertising and Communications, now known as the Office of Prescription Drug Promotion, sent a letter to Sanofi identifying promotional activities that were in violation of the FDCA and its implementing regulations on off-label promotion.

217. In particular, FDA identified promotional brochures distributed at the American Society of Clinical Oncology Annual Meeting in May 2001 that stated that Taxotere was safe and effective for first-line treatment in combination with Adriamycin such as that it was “the only taxane combination approved for first-line treatment of locally advanced or metastatic breast cancer.”

218. This was considered off-label promotion because Taxotere in combination with Adriamycin was approved by FDA only for second-line treatment—not first-line treatment—of locally advanced or metastatic breast cancer. Likewise, as explained by FDA, other taxane combinations, as well as other classes of drug combinations, were approved for this first-line treatment. FDA demanded that Sanofi “immediately cease the distribution of these and similar promotional materials.”

219. FDA sent a second warnings letter to Sanofi on December 18, 2002, concerning promotional materials at the 2002 Annual Meeting, which featured queen chess pieces and stated that Taxotere was “at the center of more strategies every day.” According to FDA, these promotional materials constituted “false or misleading promotion” which could “compromise patient survival and safety.” FDA focused on Sanofi’s claim that Taxotere resulted in “significant survival advantages,” noting that this statement was not supported by clinical trial results. FDA also noted that Sanofi underemphasized information concerning severe risks that can result from using Taxotere.

220. Sanofi responded to FDA on December 30, 2002, stating “we are discontinuing the use of these [ads], and any similar materials.” Nonetheless, Sanofi continued its false and misleading promotional and marketing activities.

221. Despite Sanofi's assurances that these and similar promotional materials would be discontinued and destroyed, FDA sent Sanofi a third warnings letter on July 17, 2003, identifying two direct-to-consumer promotional pieces that raised "similar" concerns. These two promotional ads appeared on the back of People Magazine's circulation wrap and prominently featured the slogan "The Next Move May Be the Key to Your Survival" and "It's Your Move," which again featured the queen and chess piece theme.

222. FDA found these ads to be misleading because the headline suggests that, if cancer patients want to survive breast or lung cancer, their "next move" should include Taxotere, thus implying that Taxotere is "more effective than has been demonstrated by substantial evidence or substantial clinical experience." FDA concluded that Sanofi's ads "reinforce[] the message that treatment with Taxotere will result in significant survival advantages," when the clinical data "did not necessarily represent longterm survival or a cure." FDA demanded that Sanofi submit a letter stating the status of these items (active or discontinued) as well a list of violative promotional materials.

223. Sanofi replied on August 1, 2003, assuring FDA that the two ads had been discontinued and identifying another direct-to-consumer promotional piece, similar to the two ads. The third ad, which featured the same Taxotere slogans, "*The Next Move May Be the Key to Your Survival,*" and "*It's Your Move,*" had been disseminated in "Coping," "MAAM," and "Cure" Magazines between March and July 2003 and was planned to be disseminated in these magazines in addition to "Y-Me" magazine through December 2003. Only after follow-up telephone calls did Sanofi assure FDA in an August 21, 2003 letter that it had discontinued use of this additional misleading piece.

224. FDA concluded on November 12, 2003 that these three ads likewise "misleadingly overstate[d] the survival benefits ... and impl[ied] that survival depends on treatment with Taxotere," while simultaneously "minimizing the serious and potentially life-threatening risks associated with the drug."

225. As late as January 2004, Sanofi distributed banned materials to physicians and other healthcare providers that promoted Taxotere, using materials with the same misleading slogans and substantially similar misleading information.

226. In addition, Sanofi's salespeople were directed to "cherry pick" positive clinical study results. For example, in the breast cancer setting, Sanofi trained its salespeople to downplay the results of clinical trial results and the NIH Guidelines for Adjuvant Breast Cancer, which showed that evidence of taxanes' role in the adjuvant treatment of node positive breast cancer was inconclusive. By contrast, to emphasize Taxotere's superiority over Taxol, they were also instructed to highlight preliminary results and abstracts from weaker trials. Similarly, they were trained to emphasize the lower incidence of non-lethal side effects when compared with Taxol while omitting the lethal side effect of severe neutropenia that occurs more frequently when using Taxotere.

227. In doing so, Sanofi continued to make false and misleading statements promoting the "superior efficacy" of Taxotere over the competing product paclitaxel (Taxol). In June 2008, Sanofi utilized marketing and promotional materials for Taxotere at the annual meeting for the American Society of Clinical Oncology, comparing the efficacy of Taxotere versus paclitaxel (Taxol). Specifically, Sanofi utilized a "reprint carrier," citing a clinical study published in the August 2005 edition of the Journal of Clinical Oncology. The cover of the reprint carrier claimed, among other things:

- "Taxotere demonstrated efficacy benefits vs paclitaxel"
- "This phase III study demonstrated that docetaxel is superior to paclitaxel in TTP, response duration, and OS [overall survival]."
- "Phase III trial demonstrated improved survival for Taxotere vs paclitaxel in metastatic breast cancer"

228. Sanofi's statements in the "reprint carrier" marketing the conclusions of the 2005 Journal of Clinical Oncology study were false and/or misleading in light of the 2007 and 2008 studies finding that Taxotere was not more effective than paclitaxel (Taxol) in the treatment of breast cancer.

229. Specifically, in August 2007, Cancer Treatment Reviews published a study that found no significant differences in the efficacy and outcomes obtained with Taxotere or Taxol (paclitaxel) in breast cancer treatment. Likewise, a 2008 study in the New England Journal of Medicine concluded that Taxol (paclitaxel) was more effective than Taxotere for patients undergoing standard adjuvant chemotherapy with doxorubicin and cyclophosphamide.

230. As a result of these false and misleading statements, in 2009, the FDA issued a warning letter to Sanofi citing these unsubstantiated claims of superiority over paclitaxel stating:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional reprint carrier [US.DOC.07.04.078] for Taxotere (docetaxel) Injection Concentrate, Intravenous Infusion (Taxotere) submitted under cover of Form FDA 2253 by Sanofi-Aventis (SA) and obtained at the American Society of Clinical Oncology annual meeting in June 2008. The reprint carrier includes a reprint from the Journal of Clinical Oncology, which describes the TAX 311 study. This reprint carrier is false or misleading because it presents unsubstantiated superiority claims and overstates the efficacy of Taxotere. Therefore, this material misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) and 321(n). Cf. 21 CFR 202.1(e)(6)(i), (ii) & (e)(7)(ii).

...

The reference cited in support of these claims ... does not constitute substantial evidence or substantial clinical experience to support these claims and representations because, among other factors, the study failed to demonstrate statistical significance on the primary endpoint and has not been replicated.

231. In addition, Sanofi also began indirectly promoting Taxotere through a series of direct-to-consumer television commercials that began airing in 2007. One of these commercials showed breast cancer patients slowly removing their wigs as an omniscient voice stated: “Cancer is tough but so are you. Get the facts, share the feelings, look to the future—Sanofi Aventis— because health matters and so do you.” These and other similar direct-to-consumer advertisements continued at least through 2010.

F. Sanofi Actively Sought to Hide that Taxotere Could Cause Permanent Hair Loss

232. Sanofi’s marketing efforts also affirmatively sought to minimize any association

between Taxotere and permanent alopecia.

233. According to Sanofi's Global Safety Officer for Taxotere, Sanofi knew that Taxotere could cause permanent hair loss in 2006. Despite this, Sanofi created and published in 2006 an information brochure for oncology nurses that described alopecia as "a common, yet temporary, side effect of some cancer medicines" and provided no information regarding the risk of permanent alopecia associated with Taxotere.

234. [REDACTED]

[REDACTED]

[REDACTED]

235. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

236. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

237. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

238. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

239. [REDACTED]

[REDACTED]

240. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

241. As a result of Sanofi's fraudulent concealment of the association between Taxotere and Permanent Chemotherapy Induced Alopecia, the medical community and patients, including Plaintiffs, were deprived of adequate information about the drug. Consequently, Plaintiffs were unaware of the connection between their use of Taxotere and their injury of permanent hair loss.

G. Permanent Alopecia is Devastating for Plaintiffs.

242. Research indicates that a majority of women consider alopecia the most traumatic side effect of cancer treatment. One study states that 58 percent of women preparing for chemotherapy describe alopecia as the most disturbing anticipated side effect, and that 8 percent of women may choose to forego treatment based on possible alopecia. Although baldness is the most commonly recognized form of alopecia, chemotherapy-related hair loss can extend to eyebrows, eyelashes, arm and leg hair, pubic hair, etc.

243. Women with cancer who experience alopecia, as compared with women with cancer

who do not, report lower self-esteem, poorer body image, and a lower quality of life. Alopecia can be stigmatizing and may result in anger, anxiety, embarrassment, sadness, depression, shame, helplessness, fear, and loss of sense of self. Women with alopecia may experience a loss of sense of femininity, sexuality, attractiveness, self-confidence, and womanhood. Even if hair does grow back, studies have found that these negative thoughts and feelings remain; body image tends not to return to pre-treatment levels.

244. Alopecia also alters how women interact with others and experience social situations. Alopecia symbolizes cancer identity and treatment, even when individuals wear wigs or garments to cover the hair loss. These symbols can heighten an individual's everyday awareness that she has or had cancer.

245. Hair loss alters how women recognize themselves and how others interact with them. Hair is a critical aspect of appearance that can facilitate recognition as female, young, and healthy. By contrast, loss of hair may cause others to categorize individuals as old and unhealthy. As a result, women who suffer from alopecia have a heightened awareness of their appearance during social interactions, and may be treated differently than they were before their hair loss.

246. To cope, many avoid social situations because they are nervous that others will treat them differently. These fears are not unfounded. In one study of cancer survivors, 75 percent of participants reported experiencing silent stares from others that they attributed to their "cancer appearance." Participants also reported that people they knew avoided public contact with them.

247. Hair loss can also increase risk of injury to the body. Nose hair, eyelashes, ear hair, etc. serve important bodily functions and are necessary for the protection against injury to organs critical to human senses. Hair loss in these areas places women at risk of permanent injuries.

248. Even when, unlike here, patients were warned that cancer-related hair loss may occur, cancer patients have reported feeling that they were not given adequate information about how to

manage cancer-related hair loss. This underscores the importance of healthcare providers appreciating the traumatic effect that cancer-related alopecia may have on their patients.

FIRST CLAIM FOR RELIEF
(Strict Products Liability – Failure to Warn – Against All Defendants)

249. Plaintiffs incorporate by reference each and every paragraph of this Third Amended Master Complaint as if fully set forth herein and further allege as follows.

250. At all relevant times, Defendants were in the business of designing, researching, manufacturing, testing, promoting, marketing, selling, and/or distributing pharmaceutical products, including the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate as hereinabove described that was used by Plaintiffs, or have recently acquired the entities that did the same.

251. The Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate designed, formulated, produced, manufactured, sold, marketed, distributed, supplied and/or placed into the stream of commerce by Defendants failed to provide adequate warnings to users and their healthcare providers, including Plaintiffs and Plaintiffs’ healthcare providers, of the risk of side effects associated with the use of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, particularly the risk of developing disfiguring, permanent alopecia.

252. As the holder of the Reference Listed Drug (“RLD”) for Taxotere, Sanofi supplied the labeling for Winthrop U.S.’s generic version of Taxotere.

253. The Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate designed, formulated, produced, manufactured, sold, marketed, distributed, supplied and/or placed into the stream of commerce by Defendants and ultimately administered to Plaintiffs lacked such warnings when it left Defendants’ control.

254. The risks of developing disfiguring, permanent alopecia were known to or reasonably

scientifically knowable by Defendants at the time the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate left Defendants' control.

255. Any warnings actually provided by Defendants did not sufficiently and/or accurately reflect the symptoms, type, scope, severity, and/or duration of these side effects, particularly the risks of developing disfiguring, permanent alopecia.

256. Without adequate warning of these side effects, Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate are not reasonably fit, suitable, or safe for its reasonably anticipated or intended purposes.

257. Plaintiffs were reasonably foreseeable users of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate who used the drug in reasonably anticipated manners.

258. Plaintiffs would not have used Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate had they (and their Physicians) been provided an adequate warning by Defendants of the risk of these side effects.

259. As a direct and proximate result of Defendants' failure to warn of the potentially severe adverse effects of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, Plaintiffs suffered and continue to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counseling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and impairment of the quality and enjoyment of life.

SECOND CLAIM FOR RELIEF

(Strict Products Liability for Misrepresentation – Against All Defendants)

260. Plaintiffs incorporate by reference each and every paragraph of this Third Amended Master Complaint as if fully set forth herein and further allege as follows.

261. Defendants sold the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate that Plaintiffs' healthcare providers prescribed for Plaintiffs and that Plaintiffs used.

262. Defendants were engaged in the business of selling the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate for resale, use, or consumption.

263. Defendants misrepresented facts as set forth herein concerning the character or quality of the Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate that would be material to potential prescribers and purchasers or users of the product.

264. Defendants' misrepresentations were made to potential prescribers and/or purchasers or users as members of the public at large.

265. As purchasers or users, Plaintiffs and/or their healthcare providers reasonably relied on the misrepresentations.

266. Plaintiffs were persons who would reasonably be expected to use, consume, or be affected by the Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez.

267. As a result of the foregoing acts and omissions, Defendants caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counselling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and

past, present, and future loss and impairment of the quality and enjoyment of life.

THIRD CLAIM FOR RELIEF
(Negligence – Against All Defendants)

268. Plaintiffs incorporate by reference each and every paragraph of this Third Amended Master Complaint as if fully set forth herein and further allege as follows.

269. Defendants had a duty to exercise reasonable care in the design, research, formulation, manufacture, production, marketing, testing, supply, promotion, packaging, sale, and/or distribution of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, including a duty to assure that the product would not cause users to suffer unreasonable, disfiguring, and dangerous side effects.

270. Defendants breached these duties when they put Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate into interstate commerce, unreasonably and without adequate and/or proper warning to Plaintiffs and their healthcare providers, a product that Defendants knew or should have known created a high risk of unreasonable, disfiguring, and dangerous side effects.

271. The negligence of Defendants, their agents, servants, and/or employees, included but was not limited to, the following acts and/or omissions:

- (a) Manufacturing, producing, promoting, formulating, creating, and/or designing Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate without thoroughly, adequately, and/or sufficiently testing it—including pre- clinical and clinical testing and post-marketing surveillance—for safety and fitness for use and/or its dangers and risks;
- (b) Marketing Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate to Plaintiffs, Plaintiffs’ healthcare providers, the public, and the medical and healthcare professions without adequately and correctly warning and/or disclosing the existence, severity, and duration of known or knowable side effects, including permanent alopecia;
- (c) Marketing Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate to Plaintiffs, Plaintiffs’ healthcare providers, the public, and the medical

and healthcare professions without providing adequate instructions regarding safety precautions to be observed by users, handlers, and persons who would reasonably and foreseeably come into contact with, and more particularly, use, Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez;

- (d) Advertising and recommending the use of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez; without sufficient knowledge of its safety profile;
- (e) Representing to Plaintiffs, Plaintiffs' healthcare providers, the public, and the medical and healthcare professions that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were superior to other commercially available products designed to treat the same forms of cancer Taxotere was designed to treat, when in fact they were not;
- (f) Designing, manufacturing, producing, and/or assembling Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate in a manner that was dangerous to its users;
- (g) Concealing information from Plaintiffs, Plaintiffs' healthcare providers, the public, other medical and healthcare professionals, and the FDA that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were unsafe, dangerous, and/or non-conforming with FDA regulations;
- (h) Concealing from and/or misrepresenting information to Plaintiffs, Plaintiffs' healthcare providers, other medical and healthcare professionals, and/or the FDA concerning the existence and severity of risks and dangers of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, as compared to other forms of treatment for cancer.; and
- (i) Encouraging the sale of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, either directly or indirectly, orally or in writing, to Plaintiffs and Plaintiffs' healthcare providers without warning about the need for more comprehensive and regular medical monitoring than usual to ensure early discovery of potentially serious side effects.

272. Despite the fact that Defendants knew or should have known that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate caused unreasonably dangerous side effects, Defendants continued and continue to market, manufacture, distribute, and/or sell Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate to consumers, including Plaintiffs.

273. Plaintiffs and Plaintiffs' healthcare providers were therefore forced to rely on safety information that did not accurately represent the risks and benefits associated with the use of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate as compared to other products

already commercially available to treat the same types of cancer Taxotere was designed to treat.

274. Defendants knew or should have known that consumers such as Plaintiffs would use their product and would foreseeably suffer injury as a result of Defendants' failure to exercise reasonable care, as set forth above.

275. Defendants' negligence was a proximate cause of Plaintiffs' injuries, harms, damages, and losses, in connection with the use of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, including but not limited to: past and future medical expenses; psychological counseling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement including permanent and irreversible alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and impairment of the quality and enjoyment of life.

FOURTH CLAIM FOR RELIEF
(Negligent Misrepresentation – Against All Defendants)

276. Plaintiffs incorporate by reference each and every paragraph of this Third Amended Master Complaint as if fully set forth herein and further allege as follows.

277. Defendants had a duty to represent to Plaintiffs, Plaintiffs' healthcare providers, the medical and healthcare community, and the public in general that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate had been tested and found to be safe and effective for the treatment of various forms of cancer.

278. When warning of safety and risks of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, Defendants negligently represented to Plaintiffs, Plaintiffs' healthcare providers, the medical and healthcare community, and the public in general that they had been tested and was found to be safe and/or effective for its indicated use.

279. Defendants concealed their knowledge of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, defects from Plaintiffs, Plaintiffs' healthcare providers, and the public in general and/or the medical community specifically.

280. Defendants concealed their knowledge of the defects in their products from Plaintiffs, Plaintiffs' healthcare providers, and the public in general.

281. Defendants misrepresented the novel nature of their product in order to gain a market advantage resulting in billions of dollars in revenues at the expense of vulnerable cancer victims such as Plaintiffs.

282. Defendants made these misrepresentations with the intent of defrauding and deceiving Plaintiffs, Plaintiffs' healthcare providers, the public in general, and the medical and healthcare community in particular, and were made with the intent of inducing Plaintiffs, Plaintiffs' healthcare providers, the public in general, and the medical community in particular, to recommend, dispense, and/or purchase Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate for use in the treatments of various forms of cancer, including, but not limited to, breast cancer.

283. Defendants failed to exercise ordinary and reasonable care in their representations of Taxotere while involved in its manufacture, sale, testing, quality assurance, quality control, and/or distribution into interstate commerce, and Defendants negligently misrepresented Taxotere's, Docetaxel Injection's, Docetaxel Injection Concentrate's, and Docefrez's high risks of unreasonable, dangerous side effects.

284. Defendants breached their duty in misrepresenting Taxotere's, Docetaxel Injection's, Docetaxel Injection Concentrate's, and Docefrez's, serious side effects to Plaintiffs, Plaintiffs' healthcare providers, the medical and healthcare community, the FDA, and the public in general.

285. Plaintiffs and Plaintiffs' healthcare providers reasonably relied on Defendants to fulfil their obligations to disclose all facts within their knowledge regarding the serious side effects of

Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez.

286. As a result of the foregoing acts and omissions, Defendants caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counselling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and impairment of the quality and enjoyment of life.

FIFTH CLAIM FOR RELIEF

(Fraudulent Misrepresentation – Against All Defendants)

287. Plaintiffs incorporate by reference each and every paragraph of this Third Amended Master Complaint as if fully set forth herein and further allege as follows.

288. Defendants represented to Plaintiffs, Plaintiffs' healthcare providers, the medical and healthcare community, and the public in general that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate had been tested and was found to be safe and effective for the treatment of certain forms of cancer and was free of defects that could and would cause serious side effects, including permanent and irreversible hair loss.

289. Defendants fraudulently omitted from these representations information that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate could and did cause serious side effects, including permanent and irreversible hair loss.

290. These representations were material and false.

291. Defendants made these representations and omissions:

- (a) with knowledge or belief of their falsity, and/or in the case of omissions, with knowledge or belief of falsity of the resulting statements;

- (b) positively and recklessly without knowledge of their truth or falsity;
- (c) with knowledge that they were made without any basis; and/or
- (d) without confidence in the accuracy of the representations or statements resulting from the omissions.

292. Defendants made these false representations with the intention or expectation that Plaintiffs, Plaintiffs' healthcare providers, the public in general, and the medical community in particular, would recommend, dispense, and/or purchase Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate for use in the treatments of various forms of cancer, including, but not limited to, breast cancer, all of which evidenced a callous, reckless, willful, wanton, and depraved indifference to the health, safety, and welfare of Plaintiffs.

293. At the time Defendants made the aforesaid representations, and, at the time Plaintiffs used Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, Plaintiffs and Plaintiffs' healthcare providers were unaware of the falsity of Defendants' representations, statements and/or implications and justifiably and reasonably relied upon Defendants' representations, statements, and implications, believing them to be true.

294. In reliance upon Defendants' representations, Plaintiffs and Plaintiffs' healthcare providers were induced to and did use and prescribe Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, which caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counseling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and

impairment of the quality and enjoyment of life.

SIXTH CLAIM FOR RELIEF

(Fraudulent Concealment – Against All Defendants)

295. Plaintiffs incorporate by reference each and every paragraph of this Third Amended Master Complaint as if fully set forth herein and further allege as follows.

296. At all times during the course of dealing between Defendants and Plaintiffs and Plaintiffs' healthcare providers, Defendants misrepresented the design characteristics and safety of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate for their intended use.

297. Defendants knew or were reckless in not knowing that its representations were false.

298. In representations made to Plaintiffs and Plaintiffs' healthcare providers, Defendants fraudulently concealed and intentionally omitted the following material information:

- (a) that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were not as safe as other forms of treatment for which they were marketed and sold to cancer patients;
- (b) that the risks of adverse events with Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were higher than those with other forms of treatment for which they were marketed and sold to cancer patients;
- (c) that the risks of adverse events with Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were not adequately tested and/or known by Defendants;
- (d) that Defendants were aware of dangers in Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, in addition to and above and beyond those associated with other forms of treatment for cancer patients;
- (e) that Taxotere, Docefrez, Docetaxel Injection, Docetaxel Injection Concentrate, and Docetaxel Injection Concentrate were defective in that it caused dangerous side effects as well as other severe and permanent health consequences in a much more and significant rate than other forms of treatment for cancer patients;

299. Defendants had a duty to disclose to Plaintiffs and Plaintiffs' healthcare providers the defective nature of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, and Docefrez, including, but not limited to, the heightened risks of disfiguring, permanent alopecia.

300. Defendants had sole access to material facts concerning the defective nature of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate and their propensity to cause serious and dangerous side effects, and therefore cause damage to persons who used the drugs at issue, including Plaintiffs, in particular.

301. Defendants' concealment and omissions of material fact concerning the safety of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were made purposefully, wilfully, wantonly, and/or recklessly to mislead Plaintiffs and Plaintiffs' healthcare providers into reliance on the continued use of the drugs and to cause them to purchase, prescribe, and/or dispense Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate and/or use them.

302. Defendants knew that Plaintiffs and Plaintiffs' healthcare providers had no way to determine the truth behind Defendants' concealment and omissions, including the material omissions of fact surrounding Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate set forth herein.

303. Plaintiffs and Plaintiffs' healthcare providers reasonably relied on information revealed by Defendants that negligently, fraudulently, and/or purposefully did not include facts that were concealed and/or omitted by Defendants.

304. As a result of the foregoing acts and omissions, Defendants caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counseling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and

past, present, and future loss and impairment of the quality and enjoyment of life.

SEVENTH CLAIM FOR RELIEF
(Fraud and Deceit – Against All Defendants)

305. Plaintiffs incorporate by reference each and every paragraph of this Third Amended Master Complaint as if fully set forth herein and further allege as follows.

306. Defendants committed fraud by omission in applying for and gaining patent protection for Taxotere resulting in increased sales and market penetration. This increased market penetration was the proximate cause of Plaintiffs’ exposure to the side effects of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez.

307. Defendants fraudulently claimed superior efficacy over other products designed to treat the same conditions for which Taxotere was designed to treat. These fraudulent representations were the proximate cause of Plaintiffs’ exposure to the side effects of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez.

308. As a result of Defendants’ research and testing, or lack thereof, Defendants intentionally distributed false information, including, but not limited to, assuring Plaintiffs, Plaintiffs’ healthcare providers and/or the public that Taxotere, Docefrez, Docetaxel Injection, or Docetaxel Injection Concentrate was safe and effective for use in the treatment of various forms of cancer, including breast cancer.

309. As a result of Defendants’ research and testing, or lack thereof, Defendants intentionally omitted certain results of testing and or research to Plaintiffs, Plaintiffs’ healthcare providers, healthcare professionals, and/or the public.

310. Defendants had a duty when disseminating information to Plaintiffs, Plaintiffs’ healthcare providers, and the public to disseminate truthful information.

311. Defendants had a duty when disseminating information to Plaintiffs, Plaintiffs’

healthcare providers, and the public not to deceive Plaintiffs, Plaintiffs' healthcare providers, and/or the public.

312. The information Defendants distributed to Plaintiffs, Plaintiffs' healthcare providers, and the public, including, but not limited to, reports, press releases, advertising campaigns, and other forms of media contained material misrepresentations of fact and/or omissions.

313. The information Defendants distributed to Plaintiffs, Plaintiffs' healthcare providers, and the public intentionally included false representations that Defendants' drug Taxotere was safe and effective for the treatment of various forms of cancer, including breast cancer.

314. The information Defendants distributed to Plaintiffs, Plaintiffs' healthcare providers, and the public intentionally included false representations that Defendants' drug Taxotere, Docefrez, Docetaxel Injection, or Docetaxel Injection Concentrate carried the same risks, hazards, and/or dangers as other forms of treatment for the same conditions for which Taxotere was designed to treat.

315. The information Defendants distributed to Plaintiffs, Plaintiffs' healthcare providers, and the public intentionally included false representations that Taxotere was not injurious to the health and/or safety of its intended users.

316. The information Defendants distributed to Plaintiffs, Plaintiffs' healthcare providers, and the public intentionally included false representations that Taxotere was no more injurious to the health and/or safety of its intended users as other forms of cancer treatments for which Taxotere was designed to treat.

317. These representations by Defendants were all false and misleading.

318. Defendants intentionally suppressed, ignored, and disregarded test results not favorable to Defendants and that demonstrated Taxotere was not safe as a means of treatment for certain types of cancer for which Taxotere was designed to treat.

319. Defendants intentionally made material misrepresentations to Plaintiffs, Plaintiffs'

healthcare providers, and the public in general, including the medical profession, regarding the safety of Taxotere, specifically, but not limited to, Taxotere not having dangerous and serious health and/or safety concerns.

320. Defendants intentionally made material misrepresentations to Plaintiffs, Plaintiffs' healthcare providers, and the public in general, including the medical profession, regarding the safety of Taxotere, specifically, but not limited to, Taxotere being as safe as other products designed to treat the same conditions Taxotere was designed to treat.

321. It was Defendants' intent and purpose in making these false representations to deceive and defraud Plaintiffs, Plaintiffs' healthcare providers, and/or the public and to gain the confidence of Plaintiffs, Plaintiffs' healthcare providers, the public, and/or healthcare professionals to falsely ensure the quality and fitness for use of Taxotere and induce Plaintiffs, Plaintiffs' healthcare providers, and the public, including the medical profession, to purchase, request, dispense, prescribe, recommend, and/or continue to use Taxotere.

322. Defendants made the aforementioned false claims and false representations with the intent of convincing Plaintiffs, Plaintiffs' healthcare providers, the public, and/or healthcare professionals that Taxotere, Docefrez, Docetaxel Injection, or Docetaxel Injection Concentrate was fit and safe for use as treatment for certain types of cancer, including breast cancer.

323. Defendants made the aforementioned false claims and false representations with the intent of convincing Plaintiffs, Plaintiffs' healthcare providers, the public, and/or healthcare professionals that Taxotere was fit and safe for use as treatment for certain forms of cancer and did not pose risks, dangers, or hazards above and beyond those identified and/or associated with other forms of treatment for which Taxotere, Docefrez, Docetaxel Injection, or Docetaxel Injection Concentrate was designed to treat.

324. Defendants made false claims and false representations in its documents submitted to

Plaintiffs, Plaintiffs' healthcare providers, the public, and healthcare professionals that Taxotere did not present risks related to disfigurement secondary to permanent alopecia.

325. Defendants made false claims and false representations in its documents submitted to Plaintiffs, Plaintiffs' healthcare providers, the public, and healthcare professionals that Taxotere, Docefrez, Docetaxel Injection, or Docetaxel Injection Concentrate did not present health and/or safety risks greater than other forms of treatment for the same conditions Taxotere was designed to treat.

326. Defendants made these and other representations with a pretense of actual knowledge when Defendants had no knowledge of the truth or falsity of these representations, and Defendants made these representations recklessly and without regard to the actual facts.

327. Defendants made these and other representations with the intention of deceiving and defrauding Plaintiffs and Plaintiffs' healthcare providers.

328. Defendants made these and other representations in order to induce Plaintiffs and Plaintiffs' healthcare providers to rely upon the misrepresentations.

329. Defendants' false misrepresentations caused Plaintiffs and/or Plaintiffs' healthcare providers to purchase, use, rely on, request, dispense, recommend, and/or prescribe Taxotere.

330. Defendants recklessly and intentionally falsely represented the dangerous and serious health and/or safety concerns of Taxotere to the public at large, and Plaintiffs and Plaintiffs' healthcare providers in particular, for the purpose of influencing the marketing of a product Defendants knew was dangerous and defective and/or not as safe as other alternatives, including other forms of treatment for cancer.

331. Defendants wilfully and intentionally failed to disclose, concealed, and/or suppressed the material facts regarding the dangerous and serious health and/or safety concerns related to Taxotere.

332. Defendants wilfully and intentionally failed to disclose the truth and material facts

related to Taxotere and made false representations with the purpose and design of deceiving and lulling Plaintiffs and Plaintiffs' healthcare providers into a sense of security so that Plaintiffs and Plaintiffs' healthcare providers would rely on Defendants' representations to purchase, use, dispense, prescribe, and/or recommend Taxotere.

333. Defendants, through their public relations efforts, which included, but were not limited to, public statements and press releases, knew or should have known that the public, including Plaintiffs and Plaintiffs' healthcare providers, would rely upon the information being disseminated.

334. Plaintiffs and/or Plaintiffs' healthcare providers did in fact rely on and believe Defendants' false representations to be true at the time they were made, and they relied upon Defendants' false representations and superior knowledge of how Taxotere would treat certain forms of cancer for which Taxotere was designed to treat.

335. At the time Defendants' false representations were made, Plaintiffs and/or Plaintiffs' healthcare providers did not know the truth and were not with reasonable diligence able to discover the truth with regard to the dangerous and serious health and/or safety concerns of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez.

336. Plaintiffs and their healthcare providers did not discover the true facts with respect to Defendants' false representations and the dangerous and serious health and/or safety concerns of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez, and Plaintiffs and their healthcare providers with reasonable diligence could not have discovered the true facts.

337. Had Plaintiffs and their healthcare providers known the true facts with respect to the dangerous and serious health and/or safety concerns of Taxotere, Docetaxel Injection, Docetaxel Injection Concentrate, or Docefrez, Plaintiffs would not have purchased, used, and/or relied on Defendants' drug Taxotere.

338. Defendants' aforementioned conduct constitutes fraud and deceit, and it was

committed and/or perpetrated wilfully, wantonly, and/or purposefully on Plaintiffs.

339. As a result of the foregoing acts and omissions, Defendants caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counselling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and impairment of the quality and enjoyment of life.

EIGHTH CLAIM FOR RELIEF

(Breach of Express Warranty – Against Sanofi-Related Entities Only)

340. Plaintiffs incorporate by reference each and every paragraph of this Third Amended Master Complaint as if fully set forth herein and further allege as follows.

341. Defendants expressly warranted to Plaintiffs and Plaintiffs' healthcare providers that Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate were safe and fit for use for the purposes intended, that they did not produce any dangerous side effects in excess of those risks associated with other forms of treatment for cancer, that the side effects they did produce were accurately reflected in the warnings, and that they was adequately tested.

342. These express warranties became part of the basis of the bargain Defendants made with Plaintiffs.

343. Plaintiffs and their healthcare providers relied on Defendants' express warranties in electing to purchase and use their product.

344. Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate do not conform to Defendants' express warranties, because is the drugs are not safe, were not adequately

tested, and have numerous serious side effects, which are in excess of those risks associated with other forms of treatment and which were not accurately warned about by Defendants.

345. Members of the medical community, including physicians and other healthcare providers, relied upon the representations and warranties of Defendants for use of Taxotere, Docefrez, Docetaxel Injection, and Docetaxel Injection Concentrate in recommending, prescribing, and/or dispensing the drugs at issue.

346. Defendants knew or should have known that, in fact, their representations and warranties were false, misleading, and untrue.

347. As a direct and proximate result of the foregoing breaches of warranty, Defendants caused Plaintiffs to suffer serious and dangerous side effects, severe and personal injuries that are permanent and lasting in nature, and economic and non-economic damages, harms, and losses, including, but not limited to: past and future medical expenses; psychological counseling and therapy expenses; past and future loss of earnings; past and future loss and impairment of earning capacity; permanent disfigurement, including permanent alopecia; mental anguish; severe and debilitating emotional distress; increased risk of future harm; past, present, and future physical and mental pain, suffering, and discomfort; and past, present, and future loss and impairment of the quality and enjoyment of life.

PRAYER FOR RELIEF

348. WHEREFORE, Plaintiffs pray for relief and judgement against each of the Defendants as appropriate to each cause of action alleged, as follows: compensatory damages and general damages in an amount that will conform to proof at time trial; special damages in an amount within the jurisdiction of this Court and according to proof at the time of trial; loss of earnings and impaired earning capacity according to proof at the time of trial; medical expenses, past and future, according to proof at the time of trial; for past and future mental and emotional distress, according to proof;

damages for loss of care, comfort, society, and companionship in an amount within the jurisdiction of this Court and according to proof; for punitive or exemplary damages according to proof; restitution, disgorgement of profits, and other equitable relief; attorneys' fees; for costs of suit incurred herein; for pre- and post-judgment interest as provided by law; and for such other and further relief as the Court may deem just and proper.

JURY DEMAND

349. Plaintiffs demand a trial by jury on all issues so triable.

Dated: October 8, 2018

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on October 8, 2019, I electronically filed the foregoing with the Clerk of Court by using the CM/ECF system which will send a notice of electronic filing to all counsel of record who are CM/ECF participants.

/s/ M. Palmer Lambert
M. PALMER LAMBERT

EXHIBIT D

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE
(DOCETAXEL) PRODUCTS
LIABILITY LITIGATION

CIVIL ACTION NO. 16-MD-2740 "N"
NEW ORLEANS, LOUISIANA
WEDNESDAY, AUGUST 30, 2017, 9:30 A.M.

THIS DOCUMENT RELATES TO:

ALL CASES

TRANSCRIPT OF MOTION HEARING PROCEEDINGS
HEARD BEFORE THE HONORABLE KURT D. ENGELHARDT
UNITED STATES DISTRICT JUDGE

APPEARANCES:

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OFFICIAL TRANSCRIPT

10:00:40 1 plaintiffs' counsel in formulating allegations within a Master
10:00:45 2 Long Form Complaint, as well as the administrative function of
10:00:47 3 a master complaint.

10:00:49 4 However, with that being said, specific
10:00:51 5 allegations, particularly with respect to any allegations of
10:00:54 6 fraud, should be perfected within the short form complaints
10:00:59 7 filed in the individual member cases.

10:01:01 8 However, also at this point in the litigation,
10:01:03 9 allowing plaintiffs' claims in Count 1 and Counts 3 to 7 to
10:01:10 10 proceed serves the goals of the MDL. Just as the Court noted
10:01:12 11 in the *In re: Trasylol Product Liability Litigation* -- you can
10:01:22 12 find that at 2009 Westlaw 577726 -- this Court finds that it is
10:01:28 13 in the best interest of justice to allow these claims to go
10:01:32 14 forward, and to more appropriately be addressed when we move to
10:01:38 15 the summary judgment phase of the case.

10:01:39 16 Now, with respect to Counts 2 and 8, which allege
10:01:44 17 strict liability for misrepresentation and breach of an express
10:01:47 18 warranty respectively, the Court requires additional
10:01:52 19 information from plaintiffs.

10:01:53 20 The defendants are correct in stating that the
10:01:55 21 plaintiffs have not provided any express statement by the
10:01:57 22 defendants that was either misleading or an express warranty
10:02:01 23 and relied upon by a plaintiff or a particular group of
10:02:05 24 plaintiffs.

10:02:06 25 The Court agrees that plaintiffs cannot state a

EXHIBIT E

EXPERT REPORT OF

Antonella Tosti, M.D.

October 21, 2019

I am a Fredric Brandt Endowed Professor of Dermatology at the University of Miami. I have been involved in the diagnosis and treatment of hair disorders for more than 30 years and see hair patients on a daily basis in Miami and in Europe.

I was born and trained in Italy, and I was full Professor of Dermatology at the University of Bologna until 2010. I have been full Professor at University of Miami since then.

I am among the developers of a new non-invasive method for the diagnosis of hair and scalp disorders named dermoscopy or trichoscopy, and I published the first comprehensive paper on this topic in 2006.¹ I have published many peer reviewed articles on trichoscopy, including a recent article on trichoscopy of the black scalp² and the first book/atlas on hair and scalp dermoscopy with pathological correlations in 2007.³ The book was translated in other languages and the 2nd edition of this book was published in 2015.⁴ I have been invited to teach hair disorders and trichoscopy worldwide, and have trained hundreds of dermatologists to utilize this technique to properly examine their patients.⁵

I was president and founding member of the European Hair Research Society (1989) and am now president of the American Hair Research Society and president of the International Society of Trichoscopy. I am editor of 30 Textbooks, including 6 on diagnosis and treatment of Hair Disorders.

I am the author of more than 600 peer reviewed papers, with an h-index of 58 on Scopus.⁶

My Curriculum Vitae, fee schedule, and prior deposition testimony are attached as **Exhibits A, B, and C**, respectively.

¹ Elisabeth K. Ross, Colombina Vicenzi & Antonella Tosti, *Videodermoscopy in the Evaluation of Hair and Scalp Disorders*, 55(5) J. AM. ACAD. DERMATOL. 799 (2006).

² Jorge Ocampo-Garza & Antonella Tosti, *Trichoscopy of Dark Scalp*, 5(1) SKIN APPENDAGE DISORD. 1-8 (2019).

³ Antonella Tosti, *Dermoscopy of Hair and Scalp Disorders: With Clinical and Pathological Correlations* (1st ed. 2007).

⁴ Antonella Tosti (ed.), *Dermoscopy of the Hair and Nails* (2nd ed. 2015).

⁵ Antonella Tosti, WIKIPEDIA, https://en.wikipedia.org/wiki/Antonella_Tosti (Nov. 5, 2018).

⁶ In 2005, the h-index was proposed by Jorge Hirsch, PhD and published in the *Proceedings of the National Academy of Sciences of the United States of America*. Jorge E. Hirsch, *An Index to Quantify an Individual's Scientific Research Output*, 102(46) PROC. NATL. ACAD. SCI. U.S.A. 16569 (2005).

An h-index of 58 means that I have authored at least 58 publications that have each been cited at least 58 times. Professor Hirsch reckons that after 20 years of research, an h-index of 20 is good, 40 is outstanding, and 60 is truly exceptional. The advantage of the h-index is that it combines productivity (i.e., number of papers produced) and impact (number of citations) in a single number.

Hair Anatomy and Physiology

Normal Hair

What we refer to as “hair” is in reality the “hair shaft,” which is a resilient structure produced by the hair follicle, a sophisticated organ residing in the skin. The hair shaft emerges from the scalp as a dead structure which is made up of cells that have lost their vital functions. These cells contain high concentrations of a fibrous protein called keratin. Keratin is also present in the skin, however, hair keratin, similar to nail keratin, is much stronger due to its elevated levels of cystine, a sulfur-rich amino acid.

The Hair Follicle

The hair follicle consists of two segments: the upper, or permanent segment, and the lower, or dynamic segment. The permanent segment is located in the upper dermis and is stationary during the various phases of the hair growth cycle. Whereas the dynamic segment, moves up and down in the skin throughout the various phases of the hair growth cycle.

The permanent segment of the hair follicle extends from the scalp opening to an area called “the hair bulge”, which appears as a swelling in the area where the hair erector muscle inserts the follicle. The permanent follicle is divided in two regions: the isthmus and the infundibulum. The infundibulum contains sebum, as it is connected to the sebaceous gland, and has an abundant commensal microbial flora. The isthmus contains the hair bulge that is the home of the follicle stem cells that regenerate the hair matrix at the beginning of each cycle.

The dynamic segment of the follicle includes the bulb containing the hair matrix, which is formed by the cells that actually produce the hair shaft. The hair matrix also contains melanocytes, which produce a pigment called melanin that is incorporated in the hair shaft and causes hair pigmentation. The bulb is located deep in the skin and encircles the dermal papilla, which is a specialized structure with a key role in the induction and regulation of the hair growth cycle. During the Catagen and Telogen phase (phases to be discussed in detail in the Hair Cycles section), the lower portion of the follicle involutes and moves to the upper dermis.

Types of Hair

Our body is covered with 2 types of hair: vellus hair and terminal hair. Vellus hairs are thin, short [generally < 1cm] and non-pigmented. They cover all the apparent hairless parts of our body except for the palms of the hands and soles of the feet.

Terminal hairs are long, thick, pigmented and have an internal layer called medulla. Terminal hairs are present from birth on the scalp, eyebrows and eyelashes. After puberty, they appear in the beard area, trunk and limbs of men, and in the pubic and axillary areas of both men and women. The hair follicles that produce terminal hairs are larger and located deeper within the dermis than the follicles that produce vellus hairs.

- Average terminal to vellus ratio in normal scalp is 7:1.⁷

⁷ David A. Whiting, MD, FRCP, *Diagnostic and Predictive Value of Horizontal Sections of Scalp Biopsy Specimens in Male Pattern Androgenetic Alopecia*, 28(5) J. AM. ACAD. DERMATOL. 755 (1993).

Average diameter of the shaft	
Terminal hairs of the scalp	70 μ m (60 to 84)
Vellus hairs	< 30 μ m

Terminal and vellus follicles are not entirely distinct entities, as the same follicle can transform from a vellus into a terminal follicle, and vice versa. This transformation is caused by androgens and takes place in both physiological and pathological situations. However, androgens are not the only cause and for example: transformation from vellus to terminal can be caused by trauma and drugs, transformation from terminal to vellus can be caused by drugs, radiation, toxins or other noxae.

Hair follicles in different parts of the body respond to androgens in different ways: some body areas are androgen dependent, while others are not.

Terminal hair length varies by the hair's location on the body. For example, eyelashes and eyebrows reach a maximum length of 2-3 cm, while scalp hair can grow as long as one meter.

The length and distribution of terminal hair, especially scalp hair, is determined by genetic, ethnic and gender factors. Hair shape, color, thickness, and length varies greatly due to biological diversity.

Hair Density

The density of the hair follicles is specific to the part of the body where they are located. Nearly $\frac{1}{5}$ (1,000,000) of all follicles are located on the head and on the scalp which by itself contains anywhere from 100,000 to 120,000 follicles.

Hair density depends on ethnicity, and several studies show that individuals of African descent have a significantly lower hair density as compared with Caucasians or Hispanics. A study of hair density in people of different races using phototrichogram showed an average density of 190 +/- 40 hairs/cm² in individuals of African descent (mean age 27). Total hair density in the vertex area was significantly lower in men.⁸

Using scalp biopsies, Sperling reported a density of 169-177 hairs/cm² in 20 individuals of African descent, again with men having lower density than women (mean age 36).⁹

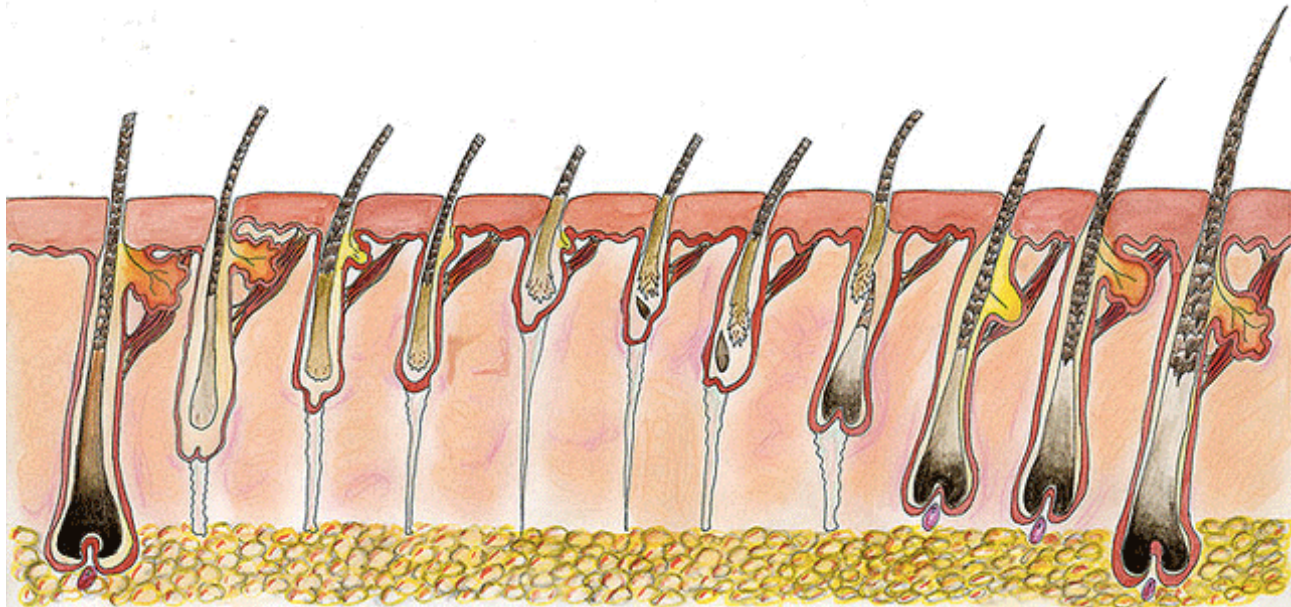
A recent study showed a density of 160 +/- 27 (frontal scalp), 149 +/- 23 (vertex), and 148 +/- 25 hairs/cm² (occipital scalp) in individuals of African descent (mean age 41.9) The study population included only 44 subjects, mostly females (32/44). They also found higher hair density in the frontal scalp.¹⁰

⁸ Geneviève Loussouarn et al., *Diversity in Human Hair Growth, Diameter, Colour and Shape. An In Vivo Study on Young Adults from 24 Different Ethnic Groups Observed in the Five Continents*, 26(2) EUR. J. DERMATOL. 144-54 (2016).

⁹ Leonard C. Sperling, MD, *Hair Density in African Americans*, 135(6) ARCH. DERMATOL. 656-68 (1999).

¹⁰ Mathew R. Birnbaum et al., *Evaluation of Hair Density in Different Ethnicities in a Healthy American Population Using Quantitative Trichoscopic Analysis*, 4 SKIN APPENDAGE DISORD. 304-07 (2018).

Hair Cycle



Anagen

Catagen

Telogen

Anagen

All hair follicles have a cyclic activity characterized by alternating periods of activity, during which they produce the hair with periods of rest.

The cycle of hair growth consists of 4 phases.

- 1) Anagen or growth phase;
- 2) Catagen or involution phase;
- 3) Telogen or resting phase;
- 4) Exogen or the shedding phase

Anagen Phase

The growth period, or Anagen Phase, is the longest of the follicular cycle. During Anagen the hair follicle actively produces the hair shaft. The cells of the hair matrix have intense mitotic and metabolic activity and rapidly divide to form the shaft. The duration of Anagen can vary considerably in different areas of the skin as well as in different individuals. For this reason, the duration of the entire cycle strictly depends on the duration of this phase of growth. Depending on which part of the body, Anagen can last anywhere from 1 month to over 7 years. The length of the hair also depends on the duration of Anagen.

In the scalp, where hair grows about 1 cm per month, the duration of Anagen usually ranges between 3 to 7 years. This is why each scalp follicle produces about 20 hairs in an individual's life. Anagen duration is shorter in males and in certain areas of the scalp, while longer in the frontal and vertex areas of the scalp. With aging the duration of the Anagen phase shortens and the hair becomes shorter and thinner.

The rate of hair growth also varies, to a small degree, in different individuals and in different body areas.

Duration of Anagen in the different body areas	
Scalp Hair	2-8 years
Eyelashes	1-6 months
Eyebrows	2-3 months

Catagen Phase

The Catagen phase or involution phase is a brief, transitory phase of the follicular cycle. During this phase, which lasts from 7 to 21 days, the follicle interrupts its mitotic activity and begins the process of involution that precedes the subsequent resting phase or Telogen.

On a normal scalp, the ratio between follicles in Anagen and follicles in Telogen is about 9 to-1 and the amount of daily hair loss ranges from 30 to 80 hairs.

Telogen Phase

Telogen corresponds to the resting or dormant phase of the cycle. The hair shaft is not lost during this phase but instead remains anchored to the scalp for the entire duration of Telogen. On the scalp, Telogen lasts about 3 months.

Exogen Phase

During Exogen, the hair shaft detaches from the follicle and sheds. Usually at this time the follicle has re-entered Anagen and a new hair is already produced. Sometimes Anagen re-entry is delayed and the follicle remains empty for a period of time. This is seen with ageing and in androgenetic alopecia. The Exogen Phase is an active phase, and the detachment of the shaft involves specific proteolytic enzymes.

Hair's Response to Damage

The follicle, as all of the body's tissues, is more susceptible to damage when its mitotic activity is high, meaning when its cells are in the process of division. Therefore, Anagen is the most delicate phase of the follicular cycle and almost all pathological conditions that cause hair loss disrupt this phase.

The follicle reacts to insults in direct proportion to the severity of the insult itself. Severe disruptions (or shocks), such as those caused by drugs utilized in cancer chemotherapy, result in mitotic arrest, when the cells of the hair matrix abruptly halt their activity and the hair is lost in a few weeks, during the Anagen Phase. As discussed in the "Telogen Effluvium" section below, a mild insult, such as a high fever, anemia or certain drugs, causes the follicle to interrupt its active growth phase and prematurely enter its resting phase. In this case, the hair will not be lost immediately, but instead hair loss will become evident about 3 months later, as 3 months is the average duration of the Telogen Phase.

Hair Loss and Alopecias

Alopecia, derived from the Greek word *alopex*, meaning fox, is a general term used to describe thinning or hair loss—a seemingly appropriate correlation as foxes lose a great amount of fur during molting.

Alopecias are classified according to shape and topographic distribution: patchy alopecias, patterned alopecias, marginal alopecias and diffuse alopecias. Also, based on the reversibility of the process, alopecias are distinguished in cicatricial or scarring alopecias and non-cicatricial or non-scarring alopecias. Patients must consult a dermatologist for proper identification of the specific disease and its cause.

Classification according to shape and topographic distribution:

- **Patchy alopecias** (present with single or multiple patches devoid of hair): alopecia areata, lichen planopilaris, discoid lupus, folliculitis decalvans, central centrifugal cicatricial alopecia, dissecting cellulitis, trichotillomania
- **Patterned alopecias** (involve temporal scalp, top of the scalp and vertex): androgenetic alopecia
- **Marginal alopecias** (involve hairline): frontal fibrosing alopecia, traction alopecia, ophiasis type of alopecia areata, androgenetic alopecia in men.
- **Diffuse alopecias** (involve the whole scalp): telogen effluvium, anagen effluvium, permanent alopecia after chemotherapy, diffuse alopecia areata

Cicatricial:	<ul style="list-style-type: none"> - Lichen planopilaris - Frontal fibrosing alopecia - Discoid lupus erythematosus - Folliculitis decalvans - Traction alopecia (late) - Central centrifugal cicatricial alopecia - Dissecting cellulitis
Non-cicatricial:	<ul style="list-style-type: none"> - Baldness (Androgenetic alopecia) - Anagen effluvium (alopecia areata, chemotherapy alopecia) - Telogen effluvium - Trichotillomania - Traction alopecia (early)

Cicatricial Alopecias (Scarring Alopecias)

Cicatricial Alopecias are a group of alopecias that are irreversible as they are caused by diseases that destroy the hair follicles permanently. In these conditions the affected hair follicles are replaced by a scar, i.e., fibrous tissue.

Cicatricial Alopecias are classified as primary or secondary depending on the mechanism of destruction of the hair follicle. In Primary Cicatricial Alopecia, the hair follicle is the main target of destruction mediated by inflammatory cells. In Secondary Cicatricial Alopecia, the hair

follicle is destroyed incidentally by non-follicle-specific processes such as burns, radiation, or infections.

The most frequent Primary Cicatricial Alopecia is Lichen Planopilaris. Its variant frontal fibrosing alopecia is becoming more and more common worldwide.

Lichen Planopilaris

Lichen Planopilaris is a relatively rare disease that often has an insidious onset characterized by persistent itching and increased hair loss. With time, the disease causes multiple scarring alopecic areas of irregular size and shape. The causes of this illness are unknown; however, researchers believe this is an autoimmune condition. An accurate diagnosis of Lichen Planopilaris requires a biopsy of the scalp, as other inflammatory diseases of the scalp, especially lupus erythematosus or folliculitis decalvans, can cause similar clinical symptoms.

Frontal Fibrosing Alopecia (FFA)

Frontal Fibrosing Alopecia typically affects postmenopausal women. In the last 10 years, frequency of this disease has been increasing worldwide. Patients complain of a slow progressive recession of the frontotemporal hairline and partial or total alopecia of the eyebrows. The hair on the arms and legs are also frequently lost.

Clinical examination reveals a band of cicatricial alopecia in the frontotemporal region. The cicatricial area is easily distinguished from the normal skin on the forehead because the hair follicles in this area have been replaced by scarred skin. Also, this skin, once covered by hair, is lighter and has less wrinkles as it has not been exposed to sunlight.

Discoïd Lupus Erythematosus

Discoïd Lupus of the scalp is more common in patients of African descent and may be associated with other cutaneous localization of the disease.

Clinical examination reveals single or multiple patches of alopecia that are often associated with hypopigmentation. The patches are red in color and show various degrees of scaling.

Folliculitis Decalvans

Folliculitis Decalvans is a severe inflammatory scalp disorder that results in cicatricial alopecia with centrifugal progression. The scalp shows multiple recurrent pustular lesions and exudative crusted areas. The inflammation subsides once the hair follicles are destroyed. It is also quite common to see multiple hairs emerging together from the scalp.

Dissecting Cellulitis

Dissecting Cellulitis is a painful inflammatory disorder that mainly affects young men of African or Hispanic descent. Frequently associated with severe acne, the affected scalp presents patches of alopecia overlying painful, fluctuant scalp nodules that often discharge pus. Its cause is unknown, dissecting cellulitis tends to run a chronic course with remissions and exacerbations, progressively leading to scarring alopecia.

Traction Alopecia

Traction Alopecia is a form of alopecia caused by prolonged tension on the hair follicle. Although reversible in early stages, long-standing Traction Alopecia can lead to permanent hair loss in the area of the scalp subject to traction. Traction Alopecia is most prevalent in women of African descent with a prevalence of about 30%. This is mainly attributed to the hair care practices (tight braids, hair weaves, and cornrows) used in this population. Clinically, patients present with symmetrical patches of alopecia of the marginal scalp, most frequently localized in the temporal regions, as these areas bear the most tension. The presence of retained hairs along the margins of the patch, termed the “fringe sign,” is commonly seen.¹¹

Central Centrifugal Cicatricial (Scarring) Alopecia (CCCA)

Central Centrifugal Cicatricial Alopecia (CCCA) is a form of chronic, progressive scarring alopecia that occurs predominantly in women of African descent. CCCA causes hair loss of the vertex of the scalp with slow centrifugal expansion. Advanced cases show a smooth and shiny scalp from the extensive destruction of follicles. There is typically no overt evidence of inflammation, but patients often complain of scalp tenderness and pain. Premature desquamation of the inner root sheath (PDIRS) is the most important histologic markers of the disease. Early CCCA and androgenetic alopecia might look similar at clinical examination but can be easily distinguished at pathology.¹²

Non-cicatricial Alopecias (Non-scarring Alopecias)

Alopecia Areata

Alopecia Areata is an autoimmune non-cicatricial alopecia. It is estimated that 2 out of 100 people will have an episode of Alopecia Areata during their lifetime. Alopecia Areata causes acute hair loss with the sudden development of round shaped bald patches. Typically, the patches are completely devoid of hair. While the patches can affect any area of the body, they are most frequently found on the scalp and beard.

Alopecia Areata in rare instances causes 100% loss of scalp hair (Alopecia Totalis) or of all scalp and body hair (Alopecia Universalis). Albeit rarely, this disease can affect only the eyelashes or eyebrows. There is also an inherited predisposition to the disease that often affects people in the same family.

Anagen Effluvium

Anagen Effluvium is the loss of hairs during the Anagen phase, the hair’s growth phase.

¹¹ Scott F. Lindsey & Antonella Tosti, *Ethnic Hair Disorders*, 47 CURR. PROBL. DERMATOL. 139 (2015).

¹² *Id.*; Erica C. Davis, M.D. et al., *Differentiating Central Centrifugal Cicatricial Alopecia and Androgenetic Alopecia in African American Men: Report of Three Cases*, 5(6) J. CLIN. AESTHET. DERMATOL. 37-40 (2012); Ncoza C. Dlova et al., *Central Centrifugal Cicatricial Alopecia: Challenges and Solutions*, 18(2) J. INVESTIG. DERMATOL. SYMP. PROC. S54-S56 (2017); Ingrid Herskovitz & Mariya Miteva, *Central Centrifugal Cicatricial Alopecia: Challenges and Solutions*, 9 CLIN. COSMET. INVESTIG. DERMATOL. 175-81 (2016); Mariya Miteva & Antonella Tosti, *Pathologic Diagnosis of Central Centrifugal Cicatricial Alopecia in Horizontal Sections*, 36(11) AM. J. DERMATOPATHOL. 859-64 (2014); Leonard C. Sperling, MC & Purnima Sau, MC, *The Follicular Degeneration Syndrome in Black Patients: “Hot Comb Alopecia” Revisited and Revised*, 128(1) ARCH. DERMATOL. 68-74 (1992).

Drug-induced Anagen Effluvium

Drug-induced Anagen Effluvium is caused by cancer chemotherapy and begins within a few weeks of drug administration,¹³ becoming more apparent with time. Hair loss is very severe, with patients potentially losing up to 1,000 strands daily. Chemotherapy-induced alopecia is usually reversible, and hair regrows normally after the of treatment with complete regrowth after approximately 6 months. The color, shape (e.g., curly, straight) and texture (e.g., fine, course) of hair can change when it regrows. Certain drugs, however, can cause a permanent/persistent alopecia.

Telogen Effluvium

Telogen Effluvium is the loss of hairs during the Telogen Phase, the hair's resting phase. Subjects complain of excessive loss when washing and brushing their hair. In the most serious cases, the subject notices hair on their clothes, pillows, food or on study books. Telogen hairs are easy to recognize because they have a proximal white tip (the root end), which is visible to the naked eye.

Telogen Effluvium is diagnosed by a variety of tests including the pull test and the hair shedding scale.

In Telogen Effluvium, hair loss occurs when the follicle ends its resting phase and starts to produce a new hair, which pushes out the old Telogen hair. This usually happens 3 months after the triggering event. For this reason, it is sometimes difficult for the patient to correlate the hair loss to the actual cause, which is never something that just happened. Generally, Telogen Effluvium is a "benign" disease, and in most cases, it does not cause evident hair thinning. Overall hair volume is commonly reduced, but there are not bald patches. A diagnosis of Telogen Effluvium requires evidence of increased hair shedding—hair density looks normal in most cases, and these patients typically bring bags of hair to the doctor to prove they have a problem. Telogen Effluvium does not cause permanent alopecia.

There are two main types of Telogen Effluvium: Acute Telogen Effluvium and Chronic Telogen Effluvium.

Acute Telogen Effluvium

Acute Telogen Effluvium is usually the result of an acute event that the subject is able to remember precisely and that, as mentioned before, has occurred approximately 3 months before the start of the hair loss. Possible causes are countless and should be researched with a detailed medical history and blood tests.

The most frequent causes of Acute Telogen Effluvium are listed below.

¹³ Ioulios Palamaras, MD et al., *Permanent Chemotherapy-Induced Alopecia: A Review*, 64(3) J. AM. ACAD. DERMATOL. 604, 604 (2011).

<ul style="list-style-type: none"> - general illnesses - anemia - high fever - viral infections - surgery - general anesthesia - acute stress - post childbirth - interruption of oral contraception - thyroid disorders - diabetes mellitus - dental treatments - weight loss - anorexia and bulimia - Vitamin D deficiency 	<ul style="list-style-type: none"> - drugs: - antidepressants - beta blockers - cholesterol-lowering drugs - antivirals - vitamin A - anabolic agents - anticoagulants - antithyroid drugs
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Drug-induced Acute Telogen Effluvium

Many drugs may interfere with the normal hair growth cycle and induce hair loss. It is important to understand that the same drug does not cause hair loss in all individuals, but as for other drug side effects only some persons have the problem.

Drug-induced Acute Telogen Effluvium occurs 2 to 4 months after initiating treatment with the hair loss ranging from 150 to more than 300 strands shed daily.

Chronic Telogen Effluvium

Chronic Telogen Effluvium is a hair condition that occurs primarily in females. The subject experiences excessive hair loss, loss of volume and thinning at of the temples. Common complaints among subjects is a much thinner ponytail, or reduced volume at the tips of the hair. These women tend to cut their hair frequently in order to create the illusion of fuller hair, or resort to wearing hair extensions for a similar effect. The number of hair follicles is not reduced.¹⁴

Androgenetic Alopecia

Androgenetic Alopecia (also called “Androgenic Alopecia”) can affect both males and females and depends on two main factors: androgen hormones and genetic predisposition.

In men, Androgen hormones, which regulate the development and maintenance of male characteristics, are the main cause of this condition. Androgens act on the genetically predisposed follicles of certain areas of the scalp (androgen dependent scalp) causing a progressive miniaturization of the hair follicle, which is a consequence of a gradual reduction of the duration of Anagen. The hair follicle produces hairs that are progressively shorter, thinner and less pigmented and do not adequately cover the scalp. The miniaturized hair follicles of

¹⁴ David A. Whiting, *Chronic Telogen Effluvium: Increased Scalp Hair Shedding in Middle-Aged Women*, 35(6) J. AM. ACAD. DERMATOL. 899 (1996).

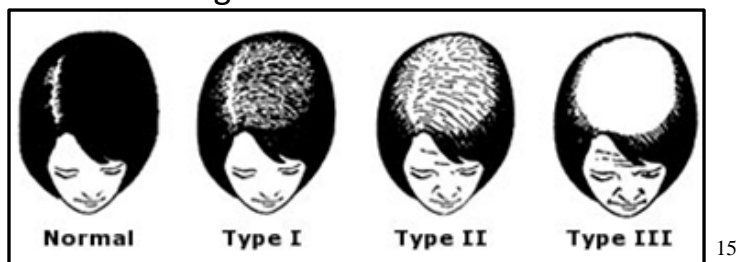
Androgenetic Alopecia look very similar to the vellus follicles that are normally present on our forehead.

Female Pattern Hair Loss

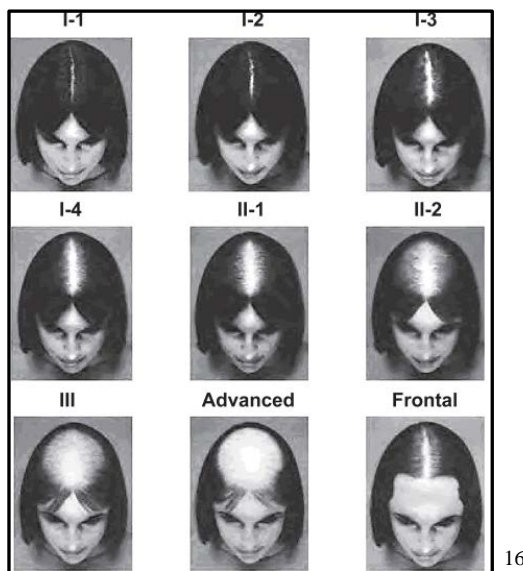
Androgenetic Alopecia in women is better known as Female Pattern Hair Loss (FPHL). Similar to Male Pattern Hair Loss, FPHL is characterized by a progressive miniaturization of the hair follicle, which affects mainly the top of the scalp with preservation of frontotemporal hairline. In severe cases the parietal and more rarely the occipital scalp may be affected.

Severity of FPHL can be assessed using the Ludwig and the Savin scale. Differently than in men FPHL involves more the top of the scalp than the vertex, which never becomes completely bald.

Ludwig Scale of Female Hair Loss



Savin Scale of Female Hair Loss



¹⁵ See Quan Q. Dinh & Rodney Sinclair, *Female Pattern Hair Loss: Current Treatment Concepts*, 2(2) CLINICAL INTERVENTIONS IN AGING 189, 190 (2007), citing Eric Ludwig, *Classification of the Types of Androgenetic Alopecia (Common Baldness) Occurring in the Female Sex*, 97 BRIT. J. DERMATOL. 247, 251 (1977).

¹⁶ See Dinh & Sinclair at 192, citing Savin RC, *Evaluating Androgenetic Alopecia in Male and Female Patients*, Kalamazoo, MI: The Upjohn Company (1994).

FPHL may be caused by hormonal therapies with androgenic effects. Hormone receptor positive breast cancer has estrogen and/or progesterone receptors. These cancers are commonly treated with endocrine therapy to lower estrogen levels, such as aromatase inhibitors, or to block estrogen's effects, such as Tamoxifen. Endocrine therapy can cause alopecia with a pattern similar to FPHL due to the miniaturization of the hair follicle.¹⁷ Endocrine therapy is not associated with follicular loss. According to a recent study, alopecia from endocrine therapy develops several months after therapy initiation (mean 16.8 months) and is moderate (grade 1) in 92% of patients.¹⁸

Permanent Alopecia After Chemotherapy (Permanent Chemotherapy-Induced Alopecia – PCIA)



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Permanent Alopecia After Chemotherapy (also known as Persistent Alopecia After Chemotherapy, Irreversible Alopecia after Chemotherapy, Permanent Chemotherapy-Induced Alopecia or PCIA) is defined as incomplete hair regrowth after chemotherapy.²⁰ The precise pathogenetic process is not known; however, it is likely due to the destruction or damage of the hair follicle or dermal papilla stem cells. This is a severe long-term side effect of chemotherapy that has been associated with high doses of chemotherapy in the context of bone marrow transplantation²¹ and, in more recent years, has been consistently identified in the context of adjuvant chemotherapy regimens containing Taxotere/docetaxel for breast cancer.²² PCIA was first reported in this context in 2001: a clinical trial investigated the efficacy and toxicity of Taxotere/docetaxel with doxorubicin and cyclophosphamide (TAC) as first-line chemotherapy

¹⁷ See Azael Freitas-Martinez, MD et al., *Endocrine Therapy-Induced Alopecia in Patients with Breast Cancer*, 154(6) JAMA DERMATOL. 670 (2018).

¹⁸ *Id.*

¹⁹ Azael Freitas-Martinez, MD et al., *Hair Disorders in Cancer Survivors*, 80(5) J. AM. ACAD. DERMATOL. 1199-1213 (2019).

²⁰ Miguel Martín et al., *Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling*, 171(3) BREAST CANCER RES. TREAT. 627-34 (2018);

²¹ See, e.g., Antonella Tosti, MD et al., *Permanent Alopecia After Busulfan Chemotherapy*, 152 BRIT. J. DERMATOL. 1056 (2005).

²² See, e.g., Ben Tallon, MBChC et al., *Permanent Chemotherapy-Induced Alopecia: Case Report and Review of the Literature*, 63(2) J. AM. ACAD. DERMATOL. 333 (2010). For the complete list of articles and abstracts I reviewed and analyzed regarding permanent chemotherapy-induced alopecia in the context of adjuvant breast cancer chemotherapy, see **Exhibit E – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy**.

for patients with metastatic breast cancer.²³ Of the 54 patients treated, long-lasting (longer than 2 years) alopecia occurred in 4 patients (7.4%).²⁴ Since then hundreds of cases have been described in the literature, and the clinical features and course of PCIA have been characterized by several retrospective and a few prospective studies.²⁵

Patients with PCIA develop Anagen Effluvium from chemotherapy and have incomplete hair regrowth 6 to 8 months after the end of chemotherapy. Patients have moderate to very severe hair thinning, with short miniaturized hairs. Hair thinning is diffuse but can be more prominent on androgen-dependent scalp regions, and the condition can be misdiagnosed as Androgenetic Alopecia at clinical examination and at pathology, even though in PCIA there is often a reduction in the follicle number in addition to miniaturization. With PCIA, thinning of eyelashes and eyebrows and other body hairs is also typical.²⁶ PCIA is graded as 1 or 2 depending on severity (necessity to wear a wig = grade 2) and psychological impact according to the Common Terminology Criteria for AEs (CTCAE) Version 4.0.²⁷

PCIA in patients receiving chemotherapy for breast cancer, outside the context of bone marrow transplantation, is a relatively new described disease: the first cases were described in 2001,²⁸ when Taxotere was introduced in the chemotherapy regimens. The other two chemotherapy agents that are commonly in Taxotere/docetaxel regimens—Adriamycin/doxorubicin (an anthracycline) and cyclophosphamide—have been on the market since 1974²⁹ and 1959.³⁰

In the treatment of breast cancer, Taxotere/docetaxel are the only chemotherapy regimens that have been consistently shown to cause Permanent Chemotherapy-Induced Alopecia.³¹ I have

²³ J.M. Nabholz et al., *Phase II Study of Docetaxel, Doxorubicin, and Cyclophosphamide as First-Line Chemotherapy for Metastatic Breast Cancer*, 19(2) J. CLIN. ONCOL. 314-21 (2001).

²⁴ *Id.* at 318.

²⁵ See, e.g., S.M. Sedlacek, *Persistent Significant Alopecia (PSA) from Adjuvant Docetaxel After Doxorubicin/Cyclophosphamide (AC) Chemotherapy in Women with Breast Cancer*, 100 BREAST CANCER RES. TREAT. s116 (2006); Ben Tallon, MBChC et al., *Permanent Chemotherapy-Induced Alopecia: Case Report and Review of the Literature*, 63(2) J. AM. ACAD. DERMATOL. 333 (2010); Antonella Tosti, MD et al., *Docetaxel and Permanent Alopecia*, 68(5) J. AM. ACAD. DERMATOL. e151 (2013); Miguel Martín et al., *Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling*, 171(3) BREAST CANCER RES. TREAT. 627-34 (2018); Danbee Kang et al., *Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study*, 23 THE ONCOLOGIST 1 (2018). For the complete list of articles and abstracts I reviewed and analyzed regarding permanent chemotherapy-induced alopecia in the context of adjuvant breast cancer chemotherapy, see **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

²⁶ Nicolas Kluger et al., *Permanent Scalp Alopecia Related to Breast Cancer Chemotherapy by Sequential Fluorouracil/Epirubicin/Cyclophosphamide (FEC) and Docetaxel: A Prospective Study of 20 Patients*, 23 Annals of Oncology 2879 (2012).

²⁷ Azael Freites-Martinez, MD et al., *Assessment of Quality of Life and Treatment Outcomes of Patients with Persistent Postchemotherapy Alopecia*, JAMA DERMATOL. (published online March 6, 2019).

²⁸ J.M. Nabholz et al., *Phase II Study of Docetaxel, Doxorubicin, and Cyclophosphamide as First-Line Chemotherapy for Metastatic Breast Cancer*, 19(2) J. CLIN. ONCOL. 314-21 (2001).

²⁹ <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=050467>.

³⁰ <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=012141>.

³¹ J.M. Nabholz et al., *Phase II Study of Docetaxel, Doxorubicin, and Cyclophosphamide as First-Line Chemotherapy for Metastatic Breast Cancer*, 19(2) J. CLIN. ONCOL. 314 (2001); Ben Tallon, MBChC et al., *Permanent Chemotherapy-Induced Alopecia: Case Report and Review of the Literature*, 63(2) J. AM. ACAD.

reviewed and analyzed 18 articles and abstracts regarding permanent chemotherapy-induced alopecia in the context of adjuvant breast cancer chemotherapy—17 of which report distinct cases of PCIA from Taxotere/docetaxel regimens, and 1 of which reports cases of PCIA from unidentified taxane (Taxotere or Taxol) regimens.³² In the adjuvant treatment of breast cancer, there are only 39 cases of permanent alopecia reported with non-taxane regimens with anthracyclines and cyclophosphamide in comparison with 497 reported cases with taxane regimens—353 of which are Taxotere/docetaxel regimens.³³ Cases of alopecia lasting more than 6 months after the end of chemotherapy have been reported with the use of Taxotere in both combination and monotherapy.³⁴ There is consistent, sufficient, and reliable evidence that Taxotere/docetaxel, when used in regimens with anthracyclines and doxorubicin, is a substantially contributing factor to PCIA.³⁵

I also co-authored an article published in 2019 in *JAMA Dermatology* that collected cases of PCIA from three cancer centers. These cases included patients who received chemotherapy for different types of cancer and not only breast cancer.³⁶ The aim of this study was evaluating the quality of life of patients with PCIA and not the frequency of PCIA from any of the regimens; therefore, this is not a prevalence study.³⁷ There were 80 cases of PCIA in regimens with Taxotere/docetaxel or Taxol/paclitaxel and 18 cases reported in regimens without Taxotere/docetaxel or Taxol/paclitaxel.³⁸ Taxotere/docetaxel and Taxol/paclitaxel are related drugs—referred to as taxanes. The study does not provide any information about the prevalence of PCIA from Taxotere/docetaxel versus Taxol/paclitaxel.

The studies I have analyzed in the aggregate demonstrate that Taxotere/docetaxel is far more commonly reported as being associated with PCIA than any other chemotherapy regimen.³⁹ I have also personally seen patients with PCIA from Taxotere/docetaxel regimens, but I have never seen patients with PCIA from Taxol/paclitaxel or other non-Taxotere regimens. I saw my first case of PCIA from Taxotere/docetaxel in 2006.

As a result of my analysis in the case, I learned that the randomized studies with Taxotere regimens for breast cancer—sponsored by the manufacturer, Sanofi, revealed that Taxotere

DERMATOL. 333 (2010); Antonella Tosti, MD et al., *Docetaxel and Permanent Alopecia*, 68(5) J. AM. ACAD. DERMATOL. e151 (2013). See **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

³² See **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

³³ See **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy. 349 cases were reported with Taxotere/docetaxel regimens, and 4 cases were reported with Taxotere/docetaxel and Taxol/paclitaxel regimens. 93 cases were reported with unidentified taxane regimens. Gun Min Kim et al., *Chemotherapy-Induced Irreversible Alopecia in Early Breast Cancer Patients*, 163 BREAST CANCER RES. TREAT. 527-33 (2017).

³⁴ H. Bourgeois, *Long Term Persistent Alopecia and Suboptimal Hair Regrowth After Adjuvant Chemotherapy for Breast Cancer*. 2009. *Long Term Persistent Alopecia and Suboptimal Hair Regrowth after Adjuvant Chemotherapy for Breast Cancer: Alert for Emerging Side Effect: French ALOPERS Observatory*, 21(8) ANNALS OF ONCOL. Viii83-84 (2010). 30(b)(6) Depositions of Michael Kopreski, MD, including all exhibits. Nanae Hangai, MD, PhD, Global Safety Officer, “Clinical Overview: Docetaxel and Permanent Alopecia” Sanofi_00829529-65.

³⁵ See **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

³⁶ Azael Freites-Martinez, MD et al., *Assessment of Quality of Life and Treatment Outcomes of Patients with Persistent Postchemotherapy Alopecia*, JAMA DERMATOL. (published online March 6, 2019).

³⁷ *Id.*

³⁸ *Id.* at E3. Among the 80 cases, 47 were paclitaxel regimens, 31 were docetaxel regimens, and 2 were paclitaxel and docetaxel regimens.

³⁹ See **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

regimens had a statistically increased rate of PCIA, when controlled for Adriamycin/doxorubicin and cyclophosphamide.⁴⁰

I was able to review Sanofi's data analysis in 2015, which concluded that Taxotere/docetaxel chemotherapy regimens can cause permanent/irreversible alopecia:

Upon review of safety database, 117 cases (5.3% of total cases of alopecia) were considered permanent alopecia (criteria: "permanent" or "irreversible" in verbatim event or longstanding (*more than 2 years*)) and have been reported in association with docetaxel treatment. . . .

Based on review of the Sanofi global pharmacovigilance database, worldwide scientific literature, clinical studies, and biological plausibility, the *cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.*⁴¹

There is consistent, sufficient, and reliable evidence that Taxotere/docetaxel, when used in in the same regimen as anthracyclines and doxorubicin, is a substantially contributing factor to PCIA.⁴²

The three studies that compared AC regimens without Taxotere/docetaxel with regimens containing Taxotere/docetaxel showed a much greater frequency and severity of PCIA in the Taxotere/docetaxel regimens. These studies demonstrate that chemotherapy regimens that include Taxotere/docetaxel are the substantial contributing factor and that Taxotere/docetaxel is the causal variable for PCIA.

*Sedlacek (2006)*⁴³

A retrospective prospective evaluation of consecutive treatment of 496 women with early-stage breast cancer was published in 2006. The patients were treated by Dr. Sedlacek from January 1994 through December of 2004. The chemotherapy regimens compared:

- Group A: 258 patients administered doxorubicin and cyclophosphamide regimens without taxanes (AC, FAC, A/CMF).
- Group B: 126 patients administered doxorubicin and cyclophosphamide plus paclitaxel/Taxol (AC/T, AT/T, AC/T dose dense, ATC, AC/Herceptin).

⁴⁰ TAX 316 Clinical Study Report (Jan. 21, 2004) at p. 5, Sanofi_02640584. TAX 316 Clinical Study Report (Sept. 9, 2010) at p. 37, Sanofi_02645236. GEICAM 9805 Clinical Study Report (Nov. 9, 2009) at 111, Sanofi_01061868.

⁴¹ Nanae Hangai, MD, PhD, Global Safety Officer, "Clinical Overview: Docetaxel and Permanent Alopecia" Sanofi_00829563 (emphasis added).

⁴² See **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy.

⁴³ S.M. Sedlacek, *Persistent Significant Alopecia (PSA) from Adjuvant Docetaxel After Doxorubicin/Cyclophosphamide (AC) Chemotherapy in Women with Breast Cancer*, 100 BREAST CANCER RES. TREAT. s116 (2006).

- Group C: 112 patients administered doxorubicin and cyclophosphamide plus docetaxel/Taxotere (AC/Tax, ATax, ACTax, AC/TaxXeloda⁴⁴, AC/Tax Herceptin⁴⁵, ATax/FAC, FAC/Tax).

The average time from the last dose of chemotherapy was 48 months (range 19 to 85 months). Persistent significant alopecia, defined as <50% hair regrowth at least one year after chemotherapy, developed in 7/112 (6.3%) of women treated with a Taxotere/docetaxel/doxorubicin/cyclophosphamide-containing regimen. All were reported to be wearing wigs. No persistent significant alopecia occurred in those treated with a Taxol/paclitaxel/doxorubicin/cyclophosphamide-containing regimen, or in those treated with a doxorubicin/cyclophosphamide regimen without a taxane.

Kang et al. (2018)⁴⁶

A prospective cohort study, from February 2012 to July 2013, was conducted of 61 consecutive patients with early stage breast cancer expected to receive adjuvant chemotherapy. The objective of the study was to estimate the long-term incidence of PCIA in patients whose hair volume and density were measured prior to chemotherapy and who were followed for three years after chemotherapy.

The patient groups received one of three regimens:

- AC (doxorubicin plus cyclophosphamide),
- FAC (fluorouracil plus cyclophosphamide and doxorubicin), or
- AC-T (Taxotere after AC).

Patients' hair was assessed prior to chemotherapy. Thereafter hair was assessed "on the first day of chemotherapy, after two cycles of chemotherapy, at 1, 3, and 6 months after completion of chemotherapy, and after 3 years after completion of chemotherapy."⁴⁷ At each visit, "hair density" and "shaft diameter" were "objectively quantified" using a dermatoscope.⁴⁸ The study defined PCIA as "absent or incomplete hair regrowth at ≥ 6 months after chemotherapy . . . if hair density or thickness was two standard deviations (SDs) or more below the baseline mean (before chemotherapy)."⁴⁹

Additionally, the investigators ruled out a number of potential risk factors: "Patients with alopecia, atopic dermatitis, psoriasis, or infectious skin diseases, as well as patients who were taking steroids, antihistamines, antidepressants, or anticonvulsants were excluded from the study."⁵⁰

⁴⁴ Xeloda (generic Capecitabine) is a chemotherapy drug that can cause temporary hair loss but has not been reported to cause permanent alopecia.

⁴⁵ Herceptin (generic Trastuzumab) is a targeted cancer drug that has not been reported to cause hair loss.

⁴⁶ Danbee Kang et al., *Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study*, 23 THE ONCOLOGIST 1 (2018).

⁴⁷ *Id.* at 2.

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ *Id.*

The study results demonstrated that Taxotere was strongly associated with PCIA: Patients with Taxotere-based treatment had “about eight times higher odds of PCIA 3 years after completion of chemotherapy (8.01; 95% CI, 1.20–53.26) adjusting for age, hair density, and thickness at diagnosis.”⁵¹ There were 23 cases of PCIA in the Taxotere group and only 3 with the cyclophosphamide and anthracycline groups.

*Martín et al. (2018)*⁵²

492 breast cancer patients with adjuvant treatment for breast cancer were studied for the prevalence of PCIA in one institution in Spain between December 2005 and May 2006. Two other institutions in Spain joined the prevalence study later to confirm the prevalence of grade 2 permanent alopecia. Grade 2 permanent alopecia was defined as severe alopecia that requires a wig after at least 18 months from the end of chemotherapy. The median follow-up of patients after the end of chemotherapy was 43 months (range 18-60 months). Grade 2 PCIA only occurred in patients with Taxotere/docetaxel regimens.

The study also addressed the issue of whether regimens containing AC or EC cause permanent alopecia in the absence of Taxotere/docetaxel. In the 306 patients receiving other chemotherapy regimens (including AC/EC regimens alone or followed by Taxol/paclitaxel), there were no cases of grade 2 permanent alopecia. The study also looked at patients receiving endocrine therapy. There were no cases of permanent alopecia (even grade 1) in patients who received tamoxifen without chemotherapy. The incidence of Taxotere/docetaxel-induced grade 2 permanent alopecia was similar in patients with (22/221, 9.96%) and without endocrine therapy (14/137, 10.2%).

Diagnostic Ladder

I have attempted to review all of the medical records of the patient. The records reviewed are listed in **Exhibit D** — Materials Consulted.

On June 4, 2019, I was able to perform an in-person evaluation of Cynthia Thibodeaux, and the examination progress notes and photographs are attached as **Exhibit F**.

During my clinical examination of Ms. Thibodeaux, I took two scalp biopsies. Subsequently I received and considered the dermatopathology report of Curtis Thompson, MD, which is attached as **Exhibit G**.

1) History

Clinical history is very important for the correct assessment of hair disorders.

Cynthia Thibodeaux is a 73-year-old woman of African descent with a Caucasian grandfather who was diagnosed with early stage breast cancer in January 2008 at the age

⁵¹ *Id.* at 3.

⁵² Miguel Martín et al., *Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling*, 171(3) BREAST CANCER RES. TREAT. 627-34 (2018).

of 61.⁵³ She enrolled in a clinical trial (NSABP trial B-40) and started neoadjuvant (pre-operative) chemotherapy on 2/12/2008.⁵⁴ Ms. Thibodeaux had 4 cycles of gemcitabine and docetaxel, followed by 4 cycles of doxorubicin (an anthracycline), and cyclophosphamide—all of which were administered with Avastin (bevacizumab), a drug that inhibits the growth of blood vessels.⁵⁵ Her last administration of chemotherapy was on 7/9/2008.⁵⁶ On 2/4/2009, Ms. Thibodeaux was prescribed Tamoxifen endocrine therapy, which she took until February 2019. History shows that she lost her hair during chemotherapy and that she had incomplete hair regrowth after that with severe permanent alopecia involving not only the scalp hair but also eyebrows, eyelashes, pubic and axillary hair. Seven months after she finished chemotherapy and before she began endocrine therapy, it was noted in Ms. Thibodeaux's medical records that some of her hair had regrown.⁵⁷ However, the regrowth was insufficient, and Ms. Thibodeaux continued to wear a wig.⁵⁸ Ms. Thibodeaux stated that when her hair grew back in February 2009, it had the appearance that it has today.⁵⁹

2) Clinical exam

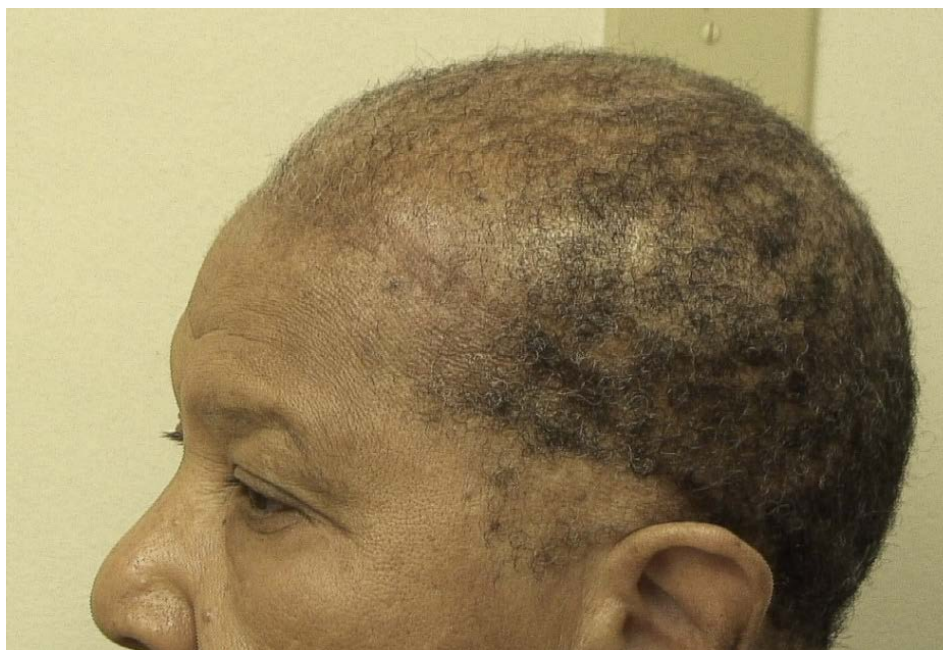


Photo of Cynthia Thibodeaux – Exhibit F – In-Person Evaluation by Dr. Tosti on June 4, 2019

⁵³ Cynthia Thibodeaux Medical Records – 1284 - Ochsner Health System 00554

⁵⁴ *Id.* at 01411.

⁵⁵ There are no case reports of PCIA from gemcitabine or bevacizumab.

⁵⁶ *Id.* at 01404.

⁵⁷ *Id.* at 01054.

⁵⁸ *Id.*

⁵⁹ Exhibit F at p. 1.



Photo of Cynthia Thibodeaux – Exhibit F – In-Person Evaluation by Dr. Tosti on June 4, 2019

A) Hair density

Hair density can be normal or reduced. It is important to compare the density of the androgen dependent scalp with the density of the occipital scalp.

Ms. Thibodeaux had reduced hair density in the whole scalp, but more prominent on androgen dependent scalp.

B) Examine the face and other hair-bearing body areas

Temporary loss of eyebrows and eyelashes is common from chemotherapy. With PCIA, thinning of eyelashes and eyebrows as well as axillary, pubic and body hair can be a long-term complication of chemotherapy.⁶⁰

Ms. Thibodeaux had thinning, but not patchy alopecia, of eyebrows and eyelashes. She had almost total alopecia of axillary hair and sparse pubic hair.

C) Look at distribution of hair loss

The most common patterns of hair loss include diffuse alopecia, patchy alopecia, patterned alopecia and marginal alopecia.

Diffuse alopecia

Diffuse scalp involvement is seen in telogen effluvium, diffuse alopecia areata, anagen effluvium

⁶⁰ Nicolas Kluger et al., *Permanent Scalp Alopecia Related to Breast Cancer Chemotherapy by Sequential Fluorouracil/Epirubicin/Cyclophosphamide (FEC) and Docetaxel: A Prospective Study of 20 Patients*, 23 *Annals of Oncology* 2879 (2012).

due to chemotherapy and permanent alopecia after chemotherapy. Severe cases of female pattern hair loss are often diffuse to the parietal but very rarely involve the frontal and occipital scalp.

Patterned alopecia

Involvement of the top of the scalp with sparing of parietal and occipital areas is typical for androgenetic alopecia. This is usually associated with involvement of the frontal hairline and the vertex in men but not in women.

The vertex is a common site of localization of several scarring alopecias including central centrifugal scarring alopecia and folliculitis decalvans.

Marginal alopecias

The marginal scalp is selectively affected in several hair disorders including traction alopecia, androgenetic alopecia, frontal fibrosing alopecia and alopecia areata.

Ms. Thibodeaux had diffuse hair thinning with prominent involvement of the androgen dependent scalp. The frontal, mid scalp, and crown show severe thinning without evidence of scarring. She had patchy alopecia of the marginal scalp bilaterally with fringe sign at the periphery.

3) Assess hair shedding

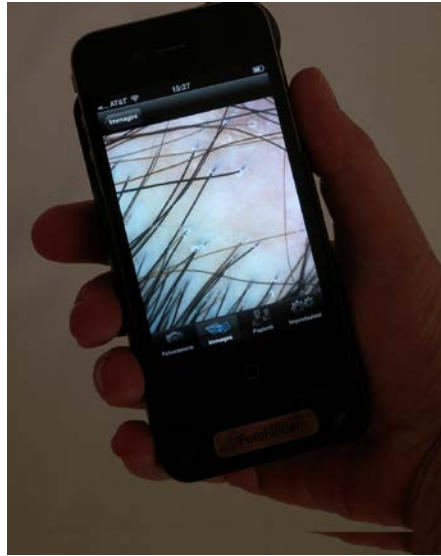
Pull test



A tuft of about 50-60 hairs is gently pulled from the scalp with the thumb and index fingers. In diffuse hair loss the test is usually performed in 4 scalp areas (including androgen dependent and non-androgen dependent scalp) and is considered positive when it produces more than 5 hairs.

Ms. Thibodeaux had a negative pull test.

4) *Trichoscopy*



Scalp dermoscopy, also known as trichoscopy is a non-invasive technique that is very useful in the evaluation of patients with hair loss. It can be performed using a manual dermoscope (x10/ x20 magnification) or a videodermoscope. Basically, it allows the physician to view and examine the scalp very closely and evaluate hair density, thickness and breakage, the presence of follicular openings and other features that are very important for diagnosing hair disorders.

Main applications of trichoscopy include distinguishing scarring from non-scarring alopecias, distinguishing androgenetic alopecia from other causes of diffuse hair loss, distinguishing frontal fibrosing alopecia from other marginal alopecias, selecting optimal biopsy site, recognizing scalp infections and infestations and recognizing hair shaft disorders.⁶¹

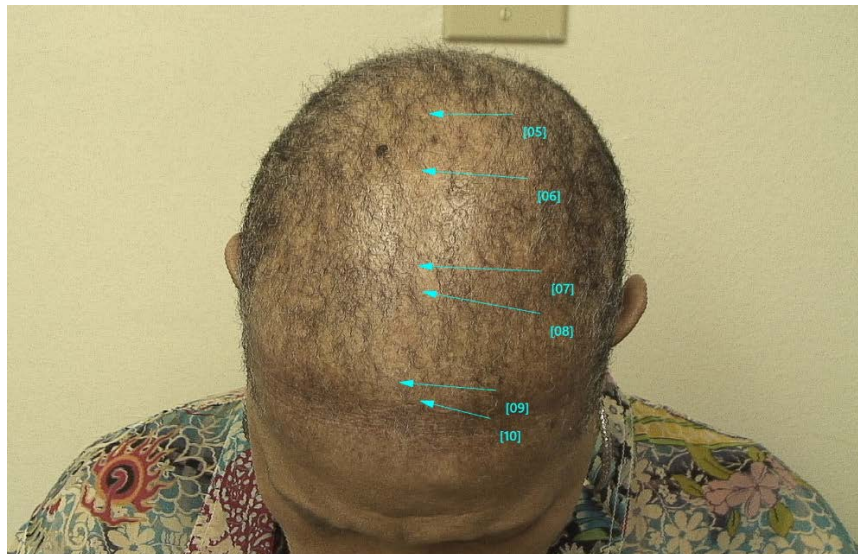


Photo of Cynthia Thibodeaux – Exhibit F – In-Person Evaluation by Dr. Tosti on June 4, 2019

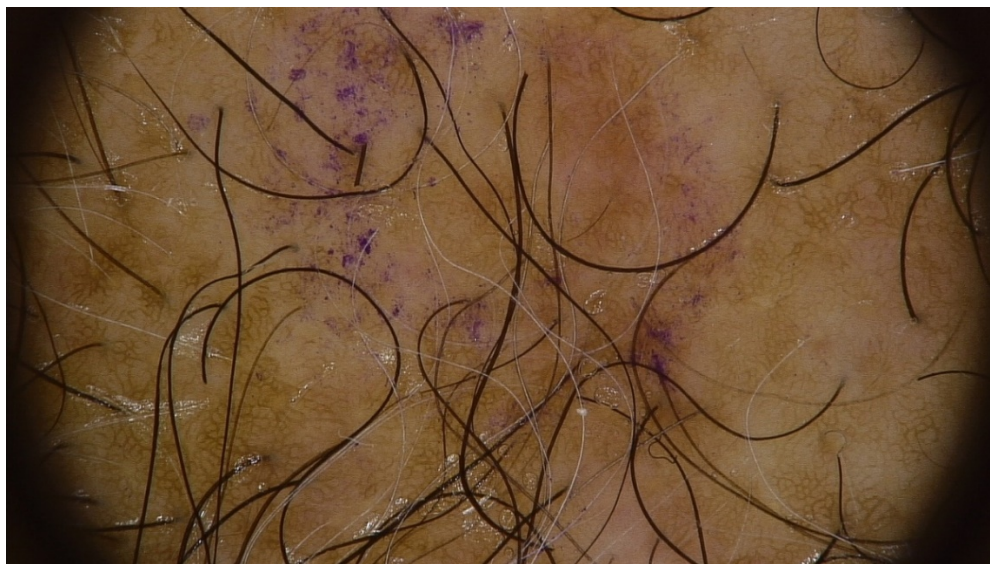
⁶¹ Antonella Tosti (ed.), *Dermoscopy of the Hair and Nails* (2nd ed. 2015).

Trichoscopy showed non-scarring alopecia, reduced follicular density and variability in the hair shaft diameter for Ms. Thibodeaux.⁶²

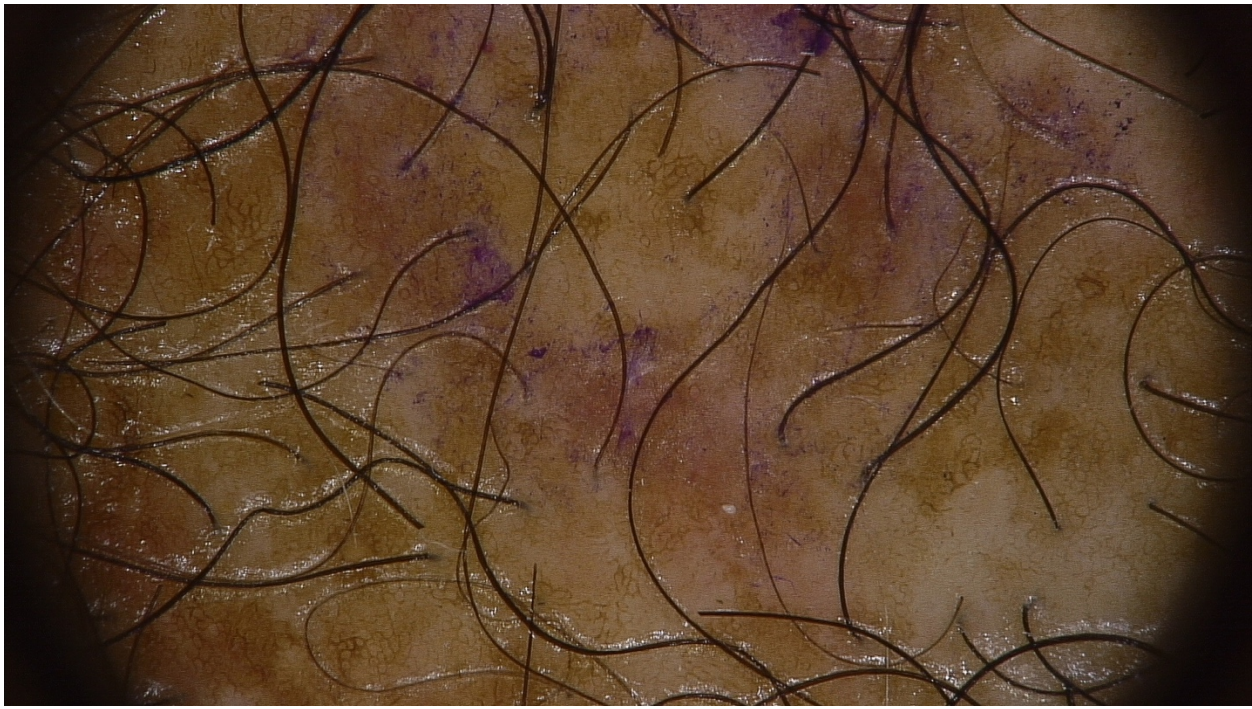
5) Take a biopsy

Definitive diagnosis of hair disorders, particularly of scarring alopecias, often requires a scalp biopsy. The size of biopsy should be 4mm. Horizontal sections are necessary to count the hairs and establish terminal to vellus and anagen to telogen ratios, which are important for diagnosis.

I took two biopsies: one from the top of the scalp at mid scalp level (Arrow 20) (marked as A) and one from the crown (Arrow 21) (marked as B).



⁶²As discussed in the “Differential” section, traction alopecia was apparent on examination of the marginal parietal scalp bilaterally.



Differential Diagnosis – Cynthia Thibodeaux

Scarring/Traction/CCCA

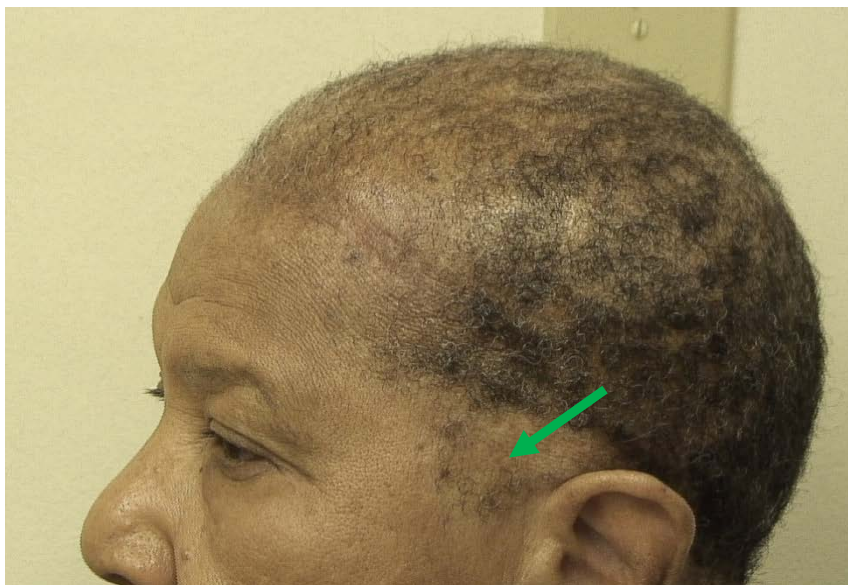


Photo of Cynthia Thibodeaux – Exhibit F – In-Person Evaluation by Dr. Tosti on June 4, 2019

Traction Alopecia

As noted in my clinical examination report, Ms. Thibodeaux had traction alopecia on examination of the marginal parietal scalp bilaterally. The pattern of traction alopecia was sufficiently apparent that I did not think further examination was required for confirmation.

Central Centrifugal Cicatricial Alopecia (CCCA)

CCCA is a scarring alopecia with characteristic dermoscopy and pathological findings.

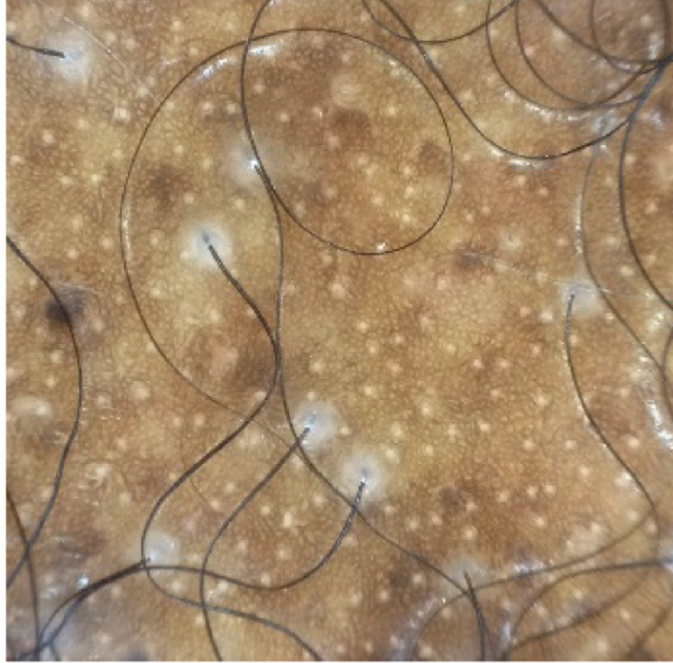
Dermoscopy of Ms. Thibodeaux's scalp (see **Exhibit F** – photos of 19 locations of dermoscopy on scalp and eyebrows) does not show characteristic findings of scarring alopecia.

Dermoscopy of scarring alopecias in the pigmented scalp shows an increased number of irregularly distributed pinpoint white dots and white patches that correspond to the areas of scarring.⁶³ In CCCA the remaining hairs are surrounded by a peripilar white/gray halo (94% of cases).⁶⁴

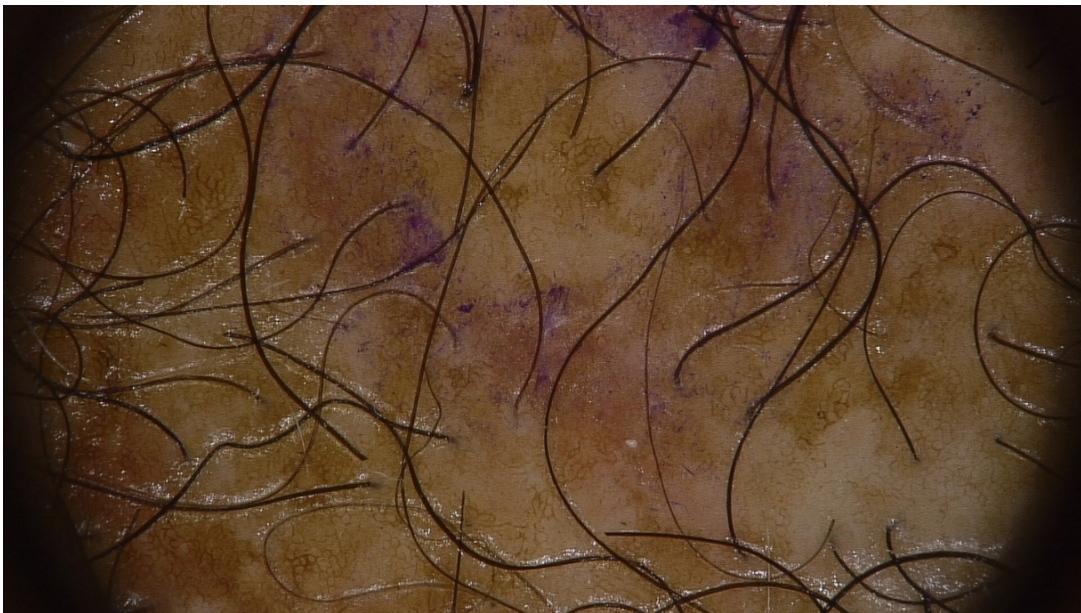
Dermoscopic examination of Ms. Thibodeaux showed reduced hair density but no signs of scarring—in particular there were not white patches or peripilar white gray halos seen in CCCA. This is consistent with the pathological findings that showed absence of fibrosis, which rules out scarring in the areas of biopsy.

⁶³ Ocampo-Garza & Tosti, Trichoscopy of Dark Scalp, 5(1) SKIN APPENDAGE DISORD. Fig. 8 (2019).

⁶⁴ Mariya Miteva, MD & Antonella Tosti, MD, *Dermoscopic Features of Central Centrifugal Cicatricial Alopecia*, 71(3) J. AM. ACAD. DERMATOL. 443 (2014).



Dermatoscope Image of Central Centrifugal Cicatricial Alopecia⁶⁵



Dermatoscope image of Cynthia Thibodeaux's scalp⁶⁶

Thinning of eyebrows and eyelashes is not consistent with CCCA. (Eyebrows are lost in FFA, which is a scarring alopecia that involves the hairline and has a very different presentation from Ms. Thibodeaux.)

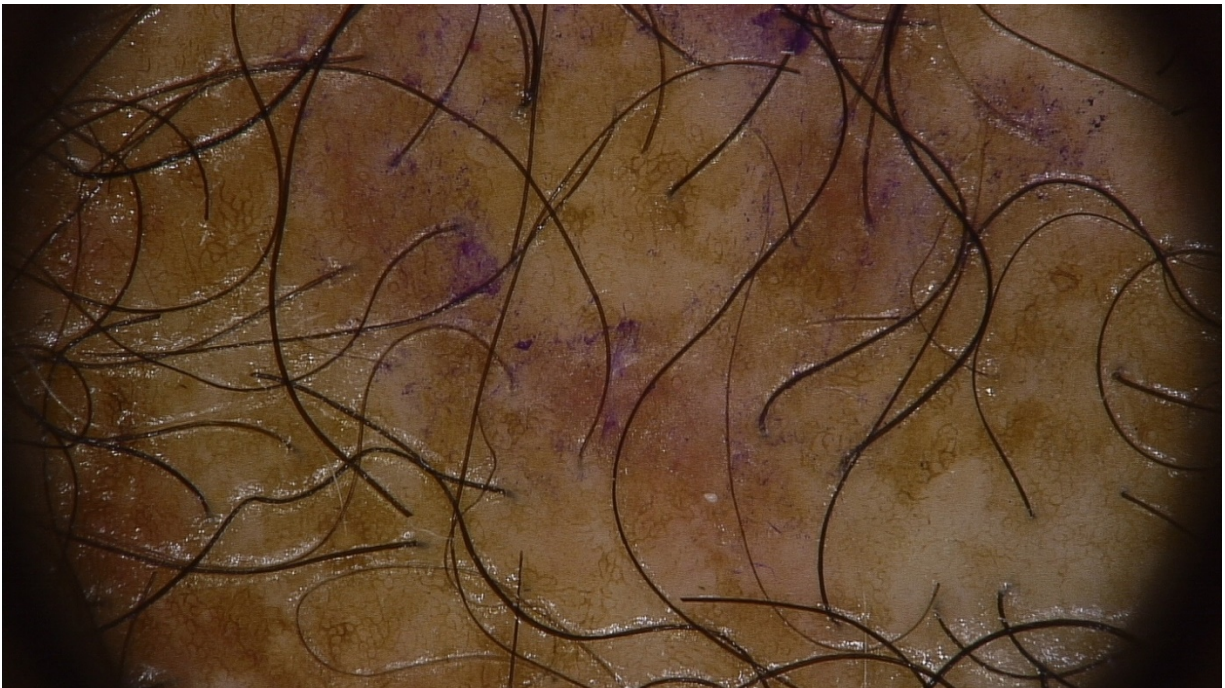
⁶⁵ Herskovitz & Miteva at 178 (Fig. 3).

⁶⁶ See **Exhibit F**.

Telogen Effluvium



Dermatoscope Image of Telogen Effluvium⁶⁷



Dermatoscope image of Cynthia Thibodeaux's scalp⁶⁸

⁶⁷ Antonella Tosti (ed.), *Dermoscopy of the Hair and Nails* (2nd ed. 2015).

⁶⁸ See **Exhibit F**.

Patients with acute telogen effluvium complain of increased shedding. In acute telogen effluvium, hair does not typically become noticeably thin though it may in more severe cases. Both acute and chronic telogen effluvium results in a positive pull test. Ms. Thibodeaux did not complain of excessive hair shedding, and her pull test was negative.

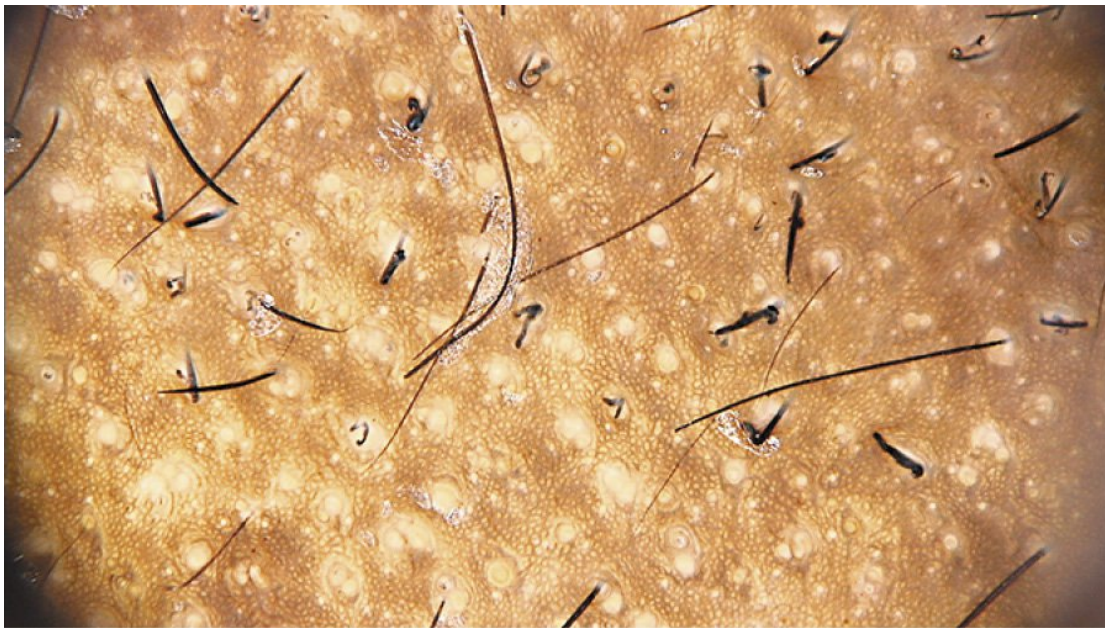
Dermoscopy of telogen effluvium shows numerous short regrowing hairs of normal thickness as the hairs that are shed are immediately replaced by new regrowing hair.

This is very different from the dermoscopy of Ms. Thibodeaux, who had very few and very thin regrowing hairs.

Although Ms. Thibodeaux is taking Synthroid/levothyroxine, which can be associated with telogen effluvium, this diagnosis is excluded by history (she is not shedding more than normal) and pull test.⁶⁹

Ms. Thibodeaux's history shows that the hair was lost during chemotherapy and never returned.

Alopecia Areata



Alopecia Areata – characteristic broken and exclamation mark hairs⁷⁰

⁶⁹ Telogen effluvium from levothyroxine has an incidence of less than 1%. Jerry Shapiro, "Chapter 5: Drug-Induced Alopecia," *Hair Loss: Principles of Diagnosis and Management of Alopecia* at 139, Table 5.2 (2002).

⁷⁰ Ocampo-Garza & Tosti, *Trichoscopy of Dark Scalp*, 5(1) SKIN APPENDAGE DISORD. Fig. 5 (2019). See also Antonella Tosti & John Gray, *Assessment of Hair and Scalp Disorders*, 12 J. INVESTIGATIVE DERMATOL. SYMPOSIUM PROCEEDINGS 23, 25 (Figure 5) (2007).



Dermoscopy image of Cynthia Thibodeaux's scalp⁷¹

The main diagnostic feature of alopecia areata is the presence of bald patches on the scalp that are completely devoid of hair. Presence of broken hairs, including “exclamation mark” hairs is typical at dermoscopy. The exclamation mark hairs have a thick dark tip. Trichoscopy of Ms. Thibodeaux did not reveal broken hairs of any type.

Alopecia areata causes sudden hair loss in round areas, leaving behind smooth patches completely devoid of hair.⁷² It might rarely cause diffuse alopecia, but in this case the pull test is positive and dermoscopy shows broken and exclamation mark hairs. Ms. Thibodeaux has diffuse hair loss without round-shaped bald patches. She has severe diffuse alopecia but no broken hairs at dermoscopy.

Ms. Thibodeaux's pull test was negative.

Anagen Effluvium

Temporary anagen effluvium is caused by a number of chemotherapy agents and scalp radiation.

It occurs during drug intake. Temporary anagen effluvium does not manifest in loss of hair follicles and is thereby distinguishable from permanent chemotherapy-induced alopecia.

A pull test would be positive in a case of temporary anagen effluvium. Ms. Thibodeaux's pull test was negative.

History is not consistent with this diagnosis as patient had chemotherapy several years ago.

⁷¹ See **Exhibit F**.

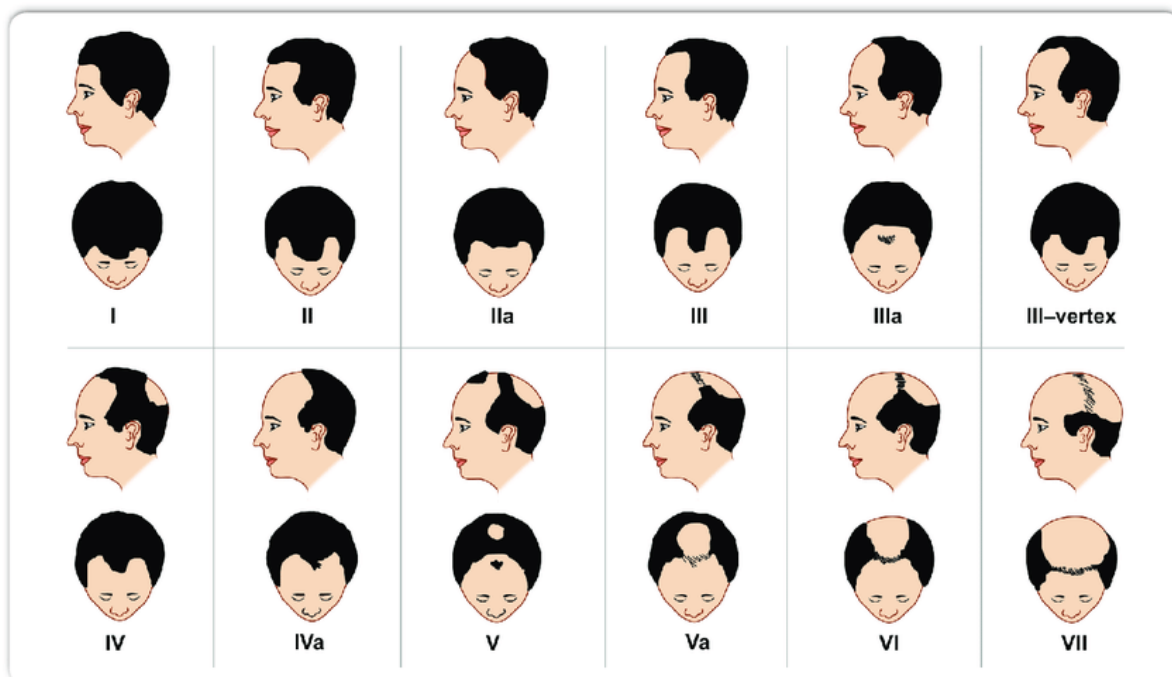
⁷² Tosti & Gray at 24.

Androgenetic Alopecia/Female Pattern Hair Loss (FPHL)

In female androgenetic alopecia (FPHL), hair thinning is not so severe. The frontal hairline is typically preserved in women. On page 11 hereinabove are illustrations of 2 scales that are utilized to grade severity of FPHL (Ludwig and Savin) and in both of them the frontal hairline is preserved. Although some women, particularly women with hormonal problems or postmenopausal women, can present with a temporal recession, they usually do not present with almost complete loss of hair in the frontal scalp. This is instead only seen in men as shown by the scale below.

In my experience androgenetic alopecia is relatively infrequent in patients of African descent, and a recent study shows that it represented only 4.5% of hair disorders in a specialist hair center in South Africa.⁷³

Norwood Hamilton Scale⁷⁴



The following categories are defined as follows: Type I: no hair loss, Type II: minor recession of the frontal hairline, Type III: further frontal hair loss, Type III vertex: significant frontal recession and hair loss from the vertex, Type IV-VI: further frontal and vertex loss, Type VII: only the occipital scalp region maintained.

⁷³ Sergio Vañó-Galván et al., *Frequency of the Types of Alopecia at Twenty-Two Specialist Hair Clinics: A Multicenter Study*, 5(5) SKIN APPENDAGE DISORD. 309-15 (2019). Men of Caucasian descent are four times more likely than men of African descent to develop androgenetic alopecia. Rodney Sinclair, *Male Pattern Androgenetic Alopecia*, 317 BRIT. MED. J. 865-69, 865 (1998).

⁷⁴ See O.T. Norwood, *Male Pattern Baldness: Classification and Incidence*, 68 SOUTH MED J. 1359 (1975).

Androgenetic alopecia involves the miniaturization of hairs, but, total follicular number is almost normal.⁷⁵ Even if hair density might slightly decrease with ageing only 5.7% of women with FPHL after the age of 70 showed a reduction in follicle number (and this was not severe: approximately 18%).⁷⁶

Ms. Thibodeaux had normal hair density before chemotherapy. She lost her hair during chemotherapy, and it never regrew enough for her to go without a wig. She developed a very severe alopecia in less than 1 year, whereas androgenetic alopecia takes place over the course of years.

Thinning of eyebrows and eyelashes is not a feature of androgenetic alopecia. Loss of pubic and axillary hair is not a feature of androgenetic alopecia.

Endocrine therapy can cause androgenetic alopecia. Ms. Thibodeaux was on Tamoxifen from 2/2009 through 2/2019. Ms. Thibodeaux started taking Tamoxifen 7 months after finishing chemotherapy. At that time, she had very sparse hair regrowth and had to wear a wig as she felt uncomfortable. She has now finished Tamoxifen therapy and did not experience any hair regrowth. Ms. Thibodeaux reports that her hair today is the same as it was just before starting Tamoxifen. The chronology of her alopecia is not consistent with this diagnosis as patients with alopecia due to endocrine therapy have normal hair regrowth after chemotherapy and then develop progressive hair thinning several months after starting endocrine therapy. Ms. Thibodeaux instead had incomplete hair regrowth with severe alopecia **before** starting endocrine therapy.

Permanent Chemotherapy-Induced Alopecia (PCIA)

Permanent Chemotherapy-Induced Alopecia (PCIA) is defined as incomplete hair regrowth 6 to 8 months after the end of chemotherapy.⁷⁷

Patients have moderate to very severe hair thinning, with short miniaturized hairs. Hair thinning is diffuse but can be more prominent on androgen-dependent scalp regions. PCIA can be misdiagnosed as Androgenetic Alopecia at clinical examination and at pathology, particularly if doctors are not familiar with this condition, which is relatively new. PCIA is also characterized by thinning of eyelashes and eyebrows and other body hairs.⁷⁸

⁷⁵ David A. Whiting, *Chronic Telogen Effluvium: Increased Scalp Hair Shedding in Middle-Aged Women*, 35(6) J. AM. ACAD. DERMATOL. 899 (1996).

⁷⁶ David A. Whiting, *How Real Is Senescent Alopecia? A Histopathologic Approach*, 29(1) CLIN. DERMATOL. 49 (2011).

⁷⁷ Miguel Martín et al., *Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling*, 171(3) BREAST CANCER RES. TREAT. 627-34 (2018); Mariya Miteva, MD et al., *Permanent Alopecia After Systemic Chemotherapy: A Clinicopathological Study of 10 Cases*, 33(4) AM. J. DERMATOPATHOL. 345 (2011).

⁷⁸ Nicolas Kluger et al., *Permanent Scalp Alopecia Related to Breast Cancer Chemotherapy by Sequential Fluorouracil/Epirubicin/Cyclophosphamide (FEC) and Docetaxel: A Prospective Study of 20 Patients*, 23 Annals of Oncology 2879 (2012).

Ms. Thibodeaux lost her hair during chemotherapy and had incomplete hair regrowth after that with severe permanent alopecia (grade 2) involving not only the scalp hair but also eyebrows, eyelashes, pubic and axillary hair. The incomplete hair regrowth was documented in her medical records seven months after she finished chemotherapy and before she began endocrine therapy. Ms. Thibodeaux's medical records report that some of her hair had regrown,⁷⁹ but the regrowth was insufficient for Ms. Thibodeaux to avoid wearing a wig.⁸⁰ Ms. Thibodeaux stated that her hair density and length in February 2009 is the same that is today.⁸¹

Ms. Thibodeaux's history, and clinical findings are consistent with a diagnosis of PCIA.

The dermatopathology report of Curtis Thompson, MD is attached as **Exhibit G**. Dr. Thompson confirms the diagnosis of "Permanent Chemotherapy-Induced Alopecia."

Based on history, clinical examination, dermoscopy, and pathology, Ms. Thibodeaux has Permanent Chemotherapy-Induced Alopecia (PCIA).

Conclusions

History, clinical examination, dermoscopy, and pathology show that Ms. Thibodeaux is affected by permanent alopecia after systemic chemotherapy (PCIA). Ms. Thibodeaux was administered Taxotere in the context of a Taxotere regimen with gemcitabine, bevacizumab, doxorubicin, and cyclophosphamide. The use of Taxotere/docetaxel with doxorubicin (an anthracycline) and cyclophosphamide is on the label for Taxotere, so it is a reasonably foreseeable use. The addition of Taxotere to her chemotherapy regimen is the cause of Ms. Thibodeaux's PCIA.

Taxotere/docetaxel has been shown to consistently cause this side effect by numerous studies. I have also personally seen patients with PCIA from Taxotere/docetaxel regimens. Doxorubicin and cyclophosphamide have been on the market since 1974 and 1959, respectively; yet the first reported cases of PCIA outside the bone marrow transplant context were in the 2000s, once Taxotere was on the market. We did not see the problem of PCIA until Taxotere was added to chemotherapy regimens. Therefore, Taxotere regimens cause PCIA. There are no cases of PCIA reported with gemcitabine or bevacizumab. In the adjuvant treatment of breast cancer, there are only 39 cases of permanent alopecia reported with non-taxane regimens with anthracyclines and cyclophosphamide in comparison with 497 reported cases with taxane regimens—353 of which are Taxotere/docetaxel regimens.⁸² The use of Taxotere in Ms. Thibodeaux's regimen was, to a reasonable degree of scientific certainty, the cause of her PCIA. Her use of Tamoxifen is not the cause of her PCIA because the history, clinical presentation, and pathology findings exclude endocrine therapy. Doxorubicin, cyclophosphamide, gemcitabine, and bevacizumab were not the

⁷⁹ *Id.* at 01054.

⁸⁰ *Id.*

⁸¹ **Exhibit F** at p. 1.

⁸² See **Exhibit E** – Articles on Permanent Alopecia Following Breast Cancer Chemotherapy. 349 cases were reported with Taxotere/docetaxel regimens, and 4 cases were reported with Taxotere/docetaxel and Taxol/paclitaxel regimens. 93 cases were reported with unidentified taxane regimens. Gun Min Kim et al., *Chemotherapy-Induced Irreversible Alopecia in Early Breast Cancer Patients*, 163 BREAST CANCER RES. TREAT. 527-33 (2017).

cause of Ms. Thibodeaux's PCIA—independent of Taxotere. Taxotere's use in the regimen was the substantial contributing factor to Ms. Thibodeaux's PCIA.

Respectfully Submitted,

A handwritten signature in blue ink, appearing to read "Antonella Tosti", written over a horizontal line.

Antonella Tosti, M.D.

October 21st, 2019

Date

EXHIBIT F

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

MDL NO.: 2740

SECTION: H

IN RE: TAXOTERE (DOCETAXEL)
PRODUCTS LIABILITY LITIGATION

This Document Relates To:

Antoinette Durden, Case No. 2:16-cv-16635;
Tanya Francis, Case No. 2:16-cv-17410;
Barbara Earnest, Case No. 2:16-cv-17144.

255 Alhambra Circle, Penthouse
Coral Gables, Florida 33134
Tuesday, 9:18 a.m. - 5:25 p.m.
December 4, 2018

VIDEOTAPED DEPOSITION OF
ANTONELLA TOSTI, M.D.

VOLUME 1
Pages 1 through 300

Taken on behalf of the Defendant before
Gina Rodriguez, RPR, CRR, Notary Public in and for
the State of Florida at Large, pursuant to Second
Amended Notice of Taking Videotaped Deposition filed
in the above cause.

1 A. It's different. I didn't check. I didn't
2 thought this could be a question.

3 And I don't check textbook for names. I
4 usually consult textbook when I need a suggestion
5 for diagnosis, for treatment. But I have the
6 textbook, and I can check all of them.

7 BY MR. SEARS:

8 Q. I think it's implied in what you said, but
9 I just want to make sure it's clear. You can't think
10 of any textbook that defines persistent alopecia,
11 right?

12 MR. SCHANKER: Objection, form.

13 A. I didn't say that. I -- I said that I
14 don't know if it's in the textbook, but I can check
15 it out and answer this question.

16 BY MR. SEARS:

17 Q. Is there a definition in the dermatological
18 community that's held to a reasonable degree of
19 medical certainty about what permanent alopecia is?

20 MR. SCHANKER: Objection, form.

21 A. I think permanent alopecia, by definition,
22 is alopecia that persists at least six months after
23 the end of chemotherapy.

24 BY MR. SEARS:

25 Q. Can you think of any textbook that defines

EXHIBIT G

Expert Report of Ellen G. Feigal, M.D.

MDL - 2740 Taxotere (Docetaxel) Products Liability Litigation

Eastern District of Louisiana United States District Court

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I am a physician, clinical researcher and former employee of the National Cancer Institute (NCI), Translational Genomics Research Institute, California Institute for Regenerative Medicine, and industry, where I held senior positions, served on the faculty of major universities including the University of California, San Francisco, and the University of California San Diego. I am currently a Partner at NDA Partners LLC and am on the Adjunct Faculty at the Sandra Day O'Connor College of Law, Arizona State University where I teach Medical Research Ethics and Law, and FDA Drug Law. I hold a Medical Degree, a Master of Science degree in molecular biology and biochemistry, a Bachelor of Science degree in Biology, have taught at several universities and have worked in senior positions for two pharmaceutical companies. I currently serve as a consultant on clinical research, product development and regulatory matters.

A copy of my curriculum vitae, including a list of publications that I have authored, is attached as Appendix A.

A list of the materials that I considered in forming my opinions is attached as Appendix B.

I have not provided testimony as an Expert Witness in trials or depositions previous to this litigation. I am being compensated in this case at the rate of \$650/hour.

I am not offering regulatory opinions about FDA requirements. I am offering opinions to a reasonable degree of medical and scientific certainty as an expert in the development of oncology drug products, the methods used to detect and evaluate safety and effectiveness, and the causal role of taxotere as it pertains to permanent alopecia. In forming my opinions set forth in this Report, I have relied on my training and experience as a physician, a hematologist/oncologist and as a clinical researcher, and my knowledge and experience with medical oncology, clinical trials and medical product development.

I. Qualifications

I am Board Certified in Internal Medicine and in Medical Oncology, have a Master of Science Degree in Biology in the fields of molecular biology and biochemistry. I graduated from the University of California Irvine with a Bachelor of Science Degree in Biology in 1976, and a Master of Science Degree in Biology (Molecular Biology and Biochemistry) from the same University in 1977. I graduated from the University of California Davis Medical School in 1981; completed my internship and first year of residency at the University of California, Davis in 1983; and completed my senior year of residency at Stanford in 1984. I completed my fellowship in hematology/oncology at the University of California, San Francisco in 1987.

Over my career, I have attained leadership positions in academia, industry and nonprofits. The theme of my career, whether in academia, industry, Federal or State government agencies or nonprofits, involves creating innovative programs and collaborations to drive translational research findings to the patients with unmet medical needs.

Assistant Professor, University of California, San Francisco (UCSF), and University of California San Diego (UCSD): 1987-1989; 1989-1991

I started my career as a physician scientist, mentoring interns, residents and medical students, taking care of AIDS patients as the epidemic emerged, in one of the major epicenters, San Francisco, at a time when there were no treatments. My patients spurred my interest to try to understand what caused their disease, particularly the AIDS-associated malignancies, to gain insights that could lead to the development of effective therapies. I began work in the laboratory trying to decipher epidemiological correlates of the disease, writing and receiving State and NIH grant support. I continued these interests of teaching, taking care of patients, and research, when I was recruited to UCSD. The AIDS epidemic also hit San Diego hard, where UCSD was a major referral center. I took charge of the medical management of patients with AIDS and cancer, including developing HIV education and treatment programs for hemophilia patients as well as attending on oncology wards, caring for patients with hematological diseases, and on the general internal medicine wards, and clinics. I was the Principal Investigator of an NIH-RO1 AIDS lymphoma grant for clinical trials in patients with AIDS-associated non-Hodgkin's Lymphoma.

National Cancer Institute (NCI): 1992 to 2004

In 1992, I began work at the National Cancer Institute (NCI) on what turned out to be the start of a 12-year period working for a mission-oriented research division in the federal government, shifting my career from an individual patient focus to creating innovative programs and initiatives with a broader national impact. During this time, I also was an attending physician in the AIDS/Oncology clinic at the NCI clinical center.

As a Senior Investigator at NCI, with responsibilities for translational research in lung cancer, head and neck cancer, and radiation therapy, I was NCI's scientific project officer for the cooperative oncology clinical trials groups focusing on those areas. The clinical trials cooperative groups enrolled over 25,000 patients per year, with several thousand per year in early phase clinical trials. The taxanes were being developed during this time period, and of note, about 80% of FDA approved drugs, including the taxanes, are engaged with the NCI during some part of their development. I asked for and was given the opportunity to create and develop an AIDS malignancy program at a national level at the NCI. At that time, the majority

of HIV associated malignancies efforts were based at the National Institute of Allergy and Infectious Diseases (NIAID) as part of the AIDS Clinical Trials Group, but I was able to create, develop, and implement AIDS malignancy clinical trials programs within the NCI's Cancer Treatment and Evaluation Program, and transferred the NIAID trials to the NCI as part of a new AIDS malignancy group. As part of the vision for putting together a comprehensive program, I developed new programs which included a multidisciplinary AIDS Malignancy Working Group, a multi-center specimen bank program for AIDS malignancy specimens, an annual National AIDS Malignancy scientific meeting, a new training program for clinical investigators, and served as a liaison to NIH-wide AIDS activities.

After five years, I became the Deputy Director of the Division of Cancer Treatment and Diagnosis (DCTD), the largest division in the NCI with an annual budget of over a billion dollars. I moved the AIDS malignancy programs I had created to be one of my responsibilities in that position, in addition to my leadership role as the Deputy Director for DCTD.

Four years later, I became and served for the next three and one-half years as the Acting Division Director assuming the primary leadership and responsibility for DCTD's programs. My responsibilities included oversight of programs in developmental therapeutics, cancer diagnostics, cancer imaging, clinical trials for evaluation of cancer therapy, radiation biology and biometrics. The position involved extensive interactions with the FDA, academia and industry in product development, and with the Centers for Medicare and Medicaid Services (CMS) on issues involving health insurance coverage and reimbursement. I created, with the intent of accelerating collaborative interactions and development, the first Interagency Council between the NCI, FDA and CMS for the joint evaluation of innovative imaging technologies. In addition, I spearheaded the collaborative work on an initiative to enhance the access of special populations to clinical trials, and provided key support for the collaborative National Lung Cancer Screening Trial and the Digital Mammography Screening Trial, comparing digital to standard film mammography, key trials that provided the evidence supporting their screening value for patients at risk of lung cancer, and of breast cancer.

In these senior positions, I interacted and was responsive to the U.S. Congress, queries from the Presidents of the United States, lawmakers, and was a peer with the leadership of major agencies including FDA and CMS. I regularly made public presentations to External Scientific Advisory Boards, and the President's (of the U.S.) Cancer Panel. I created and led the NCI's AIDS malignancy programs and created and chaired the interagency council for biomedical imaging, composed of senior leaders from the FDA, CMS and NCI. I also interacted extensively with patient advocacy groups, consumer liaison groups, heads of small and large companies; and conducted media interviews, examples of which include the science reports from the Wall

Street Journal and on live network television including the Today Show with Katie Couric, discussing the need for support for cancer clinical trials.

Vice-President: Translational Genomics Research Institute (T-Gen) and the Critical Path Institute: April 2004 to 2007

I served as the Vice President of Clinical Sciences and Deputy Scientific Director of the newly created non-profit Translational Genomics Research Institute (TGen) in Phoenix, Arizona. In this capacity I had the opportunity to work on innovative genomics technologies and their applications to patients. I was responsible for forging and developing clinical research partnerships with hospitals and clinics, major universities and research institutes across the state of Arizona in the areas of cancer, neurological and infectious diseases, and diabetes; for catalyzing and developing research collaborations across the state and nationally to enhance translational research; for strengthening clinical research interactions with the Hispanic and native American community, and for providing a robust scientific and career development environment for post-docs and TGen researchers.

My responsibilities, as part of the leadership team included, development of scientific programs, grant and contract operations, and clinical translation of Center discoveries. I assisted in fund-raising and representing the Institute in collaborations with State and University efforts, including the launching of a new medical school adjacent to the Institute.

In collaboration with TGen I spent a sabbatical year as Director, Medical Imaging and Devices, for the newly formed Critical Path Institute an independent, non-profit/tax exempt organization founded in July 2005, in order to collaborate with the Food and Drug Administration's (FDA) Critical Path Programs in the Office of the Commissioner to develop the scientific basis for more rapid and predictable regulatory decisions by FDA. I directed the medical devices and imaging programs, developed and directed the orphan diseases program to accelerate clinical studies and medical product development and opened the Phoenix satellite facility of C-Path. A memorandum of agreement between C-Path and the FDA, identified C-Path as neutral ground to help create novel programs to enable the pharmaceutical, device and biotechnology industry to safely accelerate the development of more effective treatments and diagnostics.

Adjunct Professor, UCSF School of Pharmacy: 2006 to 2011 (concurrent with other positions)

I am the founding Director of the American Course on Drug Development and Regulatory Sciences (ACDRS), a program with a two-year curriculum delivered in six one-week sessions both in Washington DC, and San Francisco. I supervised the project officer and chaired the

Executive Committee, arranged CME accreditation for the course, and supervised all aspects of the curriculum, the course examination, interactions with approximately 120 faculty and several hundred students, and strategic interactions with the FDA, and the University of Basel, Switzerland. FDA supports the program both as faculty and by sending new FDA employees as students in the course.

Chief Medical Officer, Insys Therapeutics: 2007 to 2008

Shortly after the company was founded, I became the first Chief Medical Officer of Insys Therapeutics, a small start-up privately funded pharmaceutical company that had the distinction of being the first pharmaceutical company to locate to Phoenix. I was responsible for all aspects of the clinical development of the company's products with a directed focus on supportive care oncology (such as, chronic pain, and chemotherapy-induced nausea and vomiting) and neurological diseases. I developed, designed, oversaw, and specified the analysis of two phase 1 trials, and developed, designed and launched a phase 3 trial in North America. In addition, I was responsible for the company's oversight of an investigator-initiated phase 3 trial in the UK in multiple sclerosis. The phase 3 pain management trial completed accrual in 2 years, the analyses demonstrated safety and effectiveness and FDA subsequently approved an NDA for the product.

Executive Medical Director, Amgen Inc.: April 2008 to January 2011

At Amgen I served as Executive Medical Director, Global Development at Amgen, a large biopharmaceutical company in the United States with 17,000 employees in California, alone. My primary focus was in clinical development of therapeutics in hematology/oncology. Included among the pathways of development interest were apoptosis agonists, insulin growth factor receptor antagonists, angiogenesis inhibitors, epidermal growth factor inhibitors, and RANK-ligand inhibitors. I was also responsible for formalizing and executing policy on expanded-access programs for patients across all Amgen's therapeutic areas, for the provision of investigational agents to patients in need, outside of formal clinical trials. I chaired the cross-functional team evaluating investigational agents against criteria for expanded access, led the scientific/clinical interface with patient advocacy organizations, provided the clinical guidance for the development of disease state assessment documents for the therapeutic area steering committees, and led the cross-functional teams to the company's first collaborative research and development agreement with the National Cancer Institute in Amgen's 25 year history.

Senior Vice-President: California Institute for Regenerative Medicine (CIRM): January 2011 – November 2014

CIRM is a non-profit \$3B funding agency created in 2004 by the California voters through a statewide ballot measure, with a mission to advance stem cell research for the discovery and development of disease modifying treatments and cures for patients with chronic diseases and injuries. As the Senior Vice president, for Research and Development, I played a leading role in successfully advancing CIRM funded translational programs through the preclinical and IND-enabling studies to first-in-human and early phase clinical trials across a broad range of serious medical conditions including diabetes, spinal cord injury, blinding eye diseases, heart failure, cancer, sickle cell disease, beta-thalassemia and HIV/AIDS; recruited experts of the highest caliber across the spectrum of preclinical, manufacturing, disease, stem cell biology, regulatory, clinical and commercialization to create CIRM's first external Clinical Development Advisory Panels to serve as a resource to funded investigators to better position the teams for success; played a key role in fostering and enhancing CIRM's interactions with the FDA to better elucidate the regulatory pathway for stem cell-based therapies; spearheaded the development of programs to engage industry to leverage their regulatory and business expertise, in addition to their dollars, in working with CIRM investigators; identified and engaged with NIH on the research area of induced pluripotent stem cells for disease modeling and drug discovery for neurodegenerative diseases, and developed the initiative to create and implement CIRM's collaboration with NIH in this research program.

I was responsible for the development/research teams including scientific and medical officers, a senior epidemiologist and science officer for compliance, an administrator-program manager, and co-supervising, along with the Vice-Chair of the Independent Citizens' Oversight Committee (ICOC), the Communications Director and his public communications team. My cross-functional responsibilities included work with finance, business development, legal counsel, scientific and review activities, and grants management.

I led the strategic planning for the agency across scientific, medical, economic and community goals with various stakeholders; led the assessment of the development portfolio by bringing in external experts across a broad spectrum of disciplines and worked with and reported to CIRM's governing board on a regular basis. I was a member of various committees including CIRM's Executive Committee of senior leaders and managers; Senior Staff; Senior Scientific Staff, and I directed and oversaw Development team meetings, and chaired the All-Staff monthly meetings.

I served as the Acting President during extended periods when the President was away, handling all of the leadership and management supervisory roles, including the President's role in the Institute of Medicine review of CIRM and at Board meetings that occurred during his absences.

Partner: NDA Partners LLC (NDAP): November 2014 – present

I am a Partner in NDAP, a global strategy consulting firm specializing in expert product development and regulatory advice to medical product developers. NDAP was founded in 2003 by former senior regulatory agency staff, pharmaceutical industry executives, and academic experts who have played a major role in medical product development, drug regulations and program management over the past several decades. The company has focused on improving the development efficiency and speed and commercial success rate of medical products since its founding.

Adjunct Professor, Sandra Day O'Connor College of Law, Arizona State University (ASU): Spring 2015 – present

I am an Adjunct Professor in the Sandra Day O'Connor College of Law, Arizona State University where I teach two courses: 1) Research Ethics in Human Subjects Research and the Law; and 2) FDA Drug law.

II. Scope of this Report

I have been asked to review permanent alopecia in patients with early stage breast cancer who were treated with Taxotere (docetaxel), specifically: the epidemiology, detection, diagnosis and staging of breast cancer, the treatment options, and how decisions regarding the risks and benefits of treatment options are discussed between physicians and their patients. I have also been asked to provide my assessment on the causal relationship of Taxotere to permanent chemotherapy-induced alopecia in the adjuvant treatment of patients with breast cancer.

III. Breast Cancer Epidemiology, Diagnosis and Staging:¹

Cancer: Cancer is the Latin word for crab. The ancients used the word to mean a malignancy, possibly related to the crab-like tenacity a malignant tumor shows in grasping the tissues it

¹ American Cancer Society, *Cancer Facts & Figures 2018*, available at <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf> (last visited Nov. 6, 2018).

invades. Cancer may also be called a malignancy, a malignant tumor, or a neoplasm (literally, a new growth). Cancer is not one disease, but a group of more than 100 different and distinctive diseases characterized by the uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer can start almost anywhere in the human body, which is made up of over a trillion cells. Most cancers are named for the type of cell or organ in which they start, e.g., breast cancer originates in the breast. Although the reason why the disease develops remains unknown for many cancers, there are many known causes, including lifestyle factors, such as tobacco use, alcohol consumption and obesity, and non-modifiable factors, such as gender, older age, inherited genetic mutations from parents, hormones, and immune conditions. These risk factors may act simultaneously or in sequence to initiate and/or promote cancer growth.

Breast Cancer: In the U.S. in 2018, there will be an estimated 266,120 new cases of invasive breast cancer diagnosed in women; 2,550 cases diagnosed in men; and an additional 63,960 cases of in situ breast lesions diagnosed in women.² From 2005 to 2014, the most recent 10 years for which data are available, invasive breast cancer incidence rates were stable in white women and increased slightly (by 0.3% per year) in black women.³

Symptoms and Signs of Breast Cancer: Most breast cancer is detected at an early, localized stage through mammography screening. Breast cancer, when detected early, often has no symptoms or signs. When symptoms or signs do occur, the most common sign is a lump or mass in the breast. Other symptoms may include changes to the breast, such as thickening, swelling, tenderness, skin irritation, redness, and nipple abnormalities.

Risk Factors for Breast Cancer: The strongest risk factors for breast cancer are being a woman and advancing age. Several factors that influence risk do so by modifying exposure of breast

² *Id.*

³ *Id.* In the U.S. in 2018, there will be an estimated 41,400 cases of breast cancer deaths (40,920 women, 480 men). The female breast cancer death rate peaked at 33.2 (per 100,000) in 1989, then declined by 39% to 20.3 in 2015. This progress, which is attributed to improvements in early detection (through screening, as well as increased awareness) and treatment, translates to an estimated 322,600 fewer breast cancer deaths than would have been expected if the death rate had remained at its peak. The annual percent decline from 2006 to 2015 was slightly larger for white women (1.8%) than for black women (1.5%). Adjuvant treatment is treatment given after the primary surgery to decrease the risk of local or distant (metastatic) recurrence.

tissue to reproductive hormones. Some of these risks can potentially be modified, such as being overweight or obese, the use of hormones (e.g., combined estrogen and progestin) to treat postmenopausal symptoms, lack of physical activity, and drinking alcohol. Additional risk factors affecting exposure of breast tissue to reproductive hormones include high natural levels of sex hormones, recent use of oral contraceptives, an extended menstrual history (menstrual periods that start early and/or end later in life), not having children, and having a first child after age 30. Other factors that increase risk include a family or personal history of breast or ovarian cancer; inherited genetic mutations in breast cancer susceptibility genes, such as BRCA1 or BRCA2; a history of ductal or lobular carcinoma in situ; high-dose radiation to the chest at a young age (e.g., for treatment of lymphoma), and dense breast tissue (e.g., relative proportion of glandular tissue to fatty tissue measured on a mammogram). Research suggests that other factors, such as smoking, may be a minor risk, although research is mixed and there is no consensus on smoking as a risk factor.^{4,5}

Early detection: Mammography is a low-dose x-ray imaging procedure used to screen asymptomatic women to detect breast cancer. It can also be used as a diagnostic tool to detect breast cancer in women with signs or symptoms of breast cancer, and to detect recurrences of breast cancer in those with a previous history. When used as a screening tool in asymptomatic women, early detection of breast cancer with mammography can allow for less extensive treatment and has been shown to reduce breast cancer mortality. As with any screening tool, there can be false negatives (miss detection when cancer is present) and false positives (appear abnormal in the absence of cancer). About 1 in 10 women who are screened have an abnormal

⁴ Centers for Disease Control (CDC), *What Are the Risk Factors for Breast Cancer?*, available at https://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm (last visited Sept. 2018).

⁵ The relationship between active cigarette smoking and risk of breast cancer has been extensively evaluated in both case-control and cohort studies; collectively, the data provide strong evidence against any major overall relationship, as the 2004 Report of the U.S. Surgeon General concluded the data suggest no causal relationship between active smoking and breast cancer. See U.S. Dept. of Health and Human Services, *The Health Consequences of Smoking: A Report of the Surgeon General* (2004). The question of passive or secondhand smoke exposure and risk of breast cancer was extensively reviewed in the 2006 report of the Surgeon General. After thorough evaluation of the many epidemiologic studies, the report concluded that the overall evidence is mixed and does not strongly or consistently support a causal relationship between secondhand smoke and breast cancer. See U.S. Dept. of Health and Human Services, *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General* (2006).

mammogram, and only about 5% of these women have cancer. Mammography also detects non-invasive lesions (e.g., ductal carcinoma in situ [DCIS] or lobular carcinoma in situ [LCIS]). Recently updated American Cancer Society screening guidelines for women with average risk of breast cancer, recommend that women 40 to 44 years of age have the option to begin annual mammography; those 45 to 54 should undergo annual mammography; and those 55 years of age and older may continue annual mammography or be screened on a less frequent basis every two years. If overall health is good and life expectancy is at least 10 years, guidelines recommend continued screening. For some women at high risk of breast cancer, annual magnetic resonance imaging (MRI) is recommended in addition to mammography, starting as early as 30 years of age.

Widespread adoption of screening asymptomatic women increases breast cancer detection and changes the characteristics of cancers identified by detecting more breast cancers at earlier stages. In the U.S., most patients identified have early stages of localized breast cancer detected by a screening mammogram; less commonly, patients present with a palpable mass that is either self-detected or detected by a health care provider.⁶

Diagnosis and Staging:

When breast cancer is suspected by screening mammography, patient management starts with a biopsy, which is evaluated under the microscope by the pathologist to determine if the suspicious area is malignant or benign. If malignant, the tumor is evaluated for its subtype and stage. Additionally, the subtype and staging evaluation helps determine a treatment plan; facilitate discussion between physicians and with their patients; identify patients for clinical trials and permits standardized data collection that allows for evaluation of the impact of changes in clinical practice.

The normal breast is made of tubes, called ducts, that end in a group of sacs, called lobules. Breast cancer can arise in the cells lining the ducts or lobules. Cancer cells, if they stay confined to the breast ducts or lobules, and there is no extension through the duct or lobule into surrounding tissue, is considered non-invasive carcinoma-in-situ. Once the cancer cells have grown and extended beyond the ducts or lobules, it is invasive or infiltrating cancer. The 2 main

⁶ Nancy L. Keating, MD, MPH & Lydia E. Pace, MD, MPH, *Breast Cancer Screening in 2018: Time for Shared Decision Making*, 319(17) JAMA 1814-1815 (2018).

types of breast cancer are invasive ductal and invasive lobular, based on how they look under the microscope, and in some cases, the tumor can have features of both.

Evaluating the tumor for subtype, grade and aggressiveness, and staging informs the treatment plan for the patient. Grading a tumor is part of the microscopic evaluation.⁷ Certain features can help predict how likely the cancer is to grow and spread. These features include the arrangement of the cells, whether they form tubules, whether they resemble normal breast cells, and the mitotic activity e.g., how many of the cancer cells are actively dividing. These features are assigned numbers, which are added up to assign the grade. If the numbers add up to 3 to 5, the cancer is grade 1 and well differentiated. Well-differentiated cancers have relatively normal-looking cells, divide slowly, and are arranged in small tubules for ductal cancer and cords for lobular cancer. These cancers tend to grow and spread slowly and have a better prognosis. If the numbers add up to 8 to 9, the cancer is grade 3 and poorly differentiated. Poorly differentiated cancers lack normal features, tend to divide more quickly and spread, and have a worse prognosis. If the numbers add up to 6 to 7, the cancer is grade 2 and moderately differentiated.

Key markers in subtype evaluation of the tumor include the estrogen receptor (ER), progesterone receptor (PR) and HER2/neu status. A positive finding for ER and/or PR, defined if $\geq 1\%$ of tumor cells exhibit staining, predicts benefit from endocrine therapy.⁸ HER2/neu is a receptor for a growth factor called human epidermal growth factor. A positive finding for HER2/neu overexpression, defined if $\geq 30\%$ of tumor cells exhibit strong staining on immunohistochemistry (IHC) or if gene amplification is identified by fluorescent in situ hybridization (FISH), predicts benefit from HER2/neu-directed therapy.⁹

⁷ National Cancer Institute (NCI), *Tumor Grade*, available at <https://www.cancer.gov/about-cancer/diagnosis-staging/prognosis/tumor-grade-fact-sheet> (last visited Sept. 2018).

⁸ M. Elizabeth H. Hammond et al., *American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer*, 28(16) J. CLIN. ONCOL. 2784-95 (2010).

⁹ A.C. Wolff et al., *American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer*, 131(1) ARCH. PATHOL. LAB. MED. 18-43 (2007).

The demographics of breast cancer by hormone receptor (ER/PR) and HER2 status are provided in Table 1.¹⁰

ER/PR	HER2	Percentage
Positive	Negative	68.9%
Positive	Positive	10.2%
Negative	Positive	7.5%
Negative	Negative	13.4%

Gene profiling, and specific genetic tests on the tumor for the probability of breast cancer recurrence are also used and can guide to help inform treatment decisions, including the Mammaprint and Oncotype DX assays. Oncotype DX assays have been used to predict the probability of benefit from adjuvant chemotherapy in ER-positive node-negative disease and in postmenopausal women with ER-positive, axillary node positive disease.¹¹ These markers may be used to assist in making more informed treatment decisions regarding whether to use chemotherapy, particularly in low-risk patients with ER positive, HER2/neu-negative disease.^{12,13}

Cancer is staged with the American Joint Committee on Cancer (AJCC) staging system TNM, which assesses cancer growth and spread by the extent of the tumor (T), absence or presence of lymph nodes (N), and the absence or presence of distant metastases (M). The T category (T0, Tis, T1, T2, T3, or T4) is based on the size of the tumor and whether it has spread to the skin

¹⁰ Adedayo A. Onitilo, MD et al., *Breast Cancer Subtypes Based on ER/PR and Her2 Expression: Comparison of Clinicopathologic Features and Survival*, 7(1/2) CLINICAL MEDICINE & RESEARCH 4-13 (2009).

¹¹ Prof. Kathy S. Albain, MD et al., *Prognostic and Predictive Value of the 21-Gene Recurrence Score Assay in Postmenopausal Women with Node-Positive, Oestrogen-Receptor-Positive Breast Cancer on Chemotherapy: A Retrospective Analysis of a Randomized Trial*, 11(1) LANCET ONCOL. 55-65 (2010).

¹² J.A. Sparano & L.J. Solin, *Defining the Clinical Utility of Gene Expression Assays in Breast Cancer: the Intersection of Science and Art in Clinical Decision Making*, 28(10) J. CLIN. ONCOL. 1625-27 (2010).

¹³ L. Harris et al., *American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer*, 25(33) J. CLIN. ONCOL. 5287-312 (2007).

over the breast or to the chest wall under the breast. Higher T numbers mean a larger tumor and/or wider spread to tissues near the breast. The N category (N0, N1, N2, or N3) indicates whether the cancer has spread to lymph nodes near the breast and, if so, how many lymph nodes are affected. Higher numbers after the N indicate more lymph node involvement by cancer. The M category (M0, M1) is usually based on the results of lab and imaging. Once TNM is determined, a stage of 0, I, II, III or IV is assigned.¹⁴ Stage 0 is non-invasive (in situ) cancer; stage I is a small tumor in the breast only; stage II is a tumor in the breast over 2cm in size and/or with lymph nodes involved; stage III is a larger tumor (more than 5 cm in size) in the breast or with more than 3 lymph nodes involved with tumor, and stage IV is spread of the tumor to other parts of the body, often in bones, lungs, liver, skin and brain. Imaging may be indicated if there are signs, symptoms, or laboratory abnormalities suggesting distant metastases.

The stage distribution of breast cancer is approximately 62% localized (tumors less than 5 cm and no lymph node involvement), 31% regional (lymph node involvement), and 6% distant (metastatic).¹⁵

Advances in molecular diagnostics, and more tailored treatments have led to a recent revision of the American Joint Committee on Cancer (AJCC) staging system for breast cancer that allows for more accurate staging.¹⁶ The recent revision has incorporated biologic variables, already in use for treatment planning e.g., grade, ER, PR and HER2 status, and multigene panels, into the conventional anatomic extent of disease defined by TNM.

The receptor status e.g., whether ER, PR and HER2 positive or negative and the staging, whether stage 0, I, II, III or IV and their subtypes, and molecular markers, such as Oncotype Dx or MammaPrint, can be used to help assess prognosis and guide discussions of the physician and their patient in making treatment decisions.

¹⁴ Clinical stage is based on examining the patient and reviewing the lab/imaging studies after the initial diagnostic biopsy; Pathologic stage is based on tumor and lymph node assessment from the surgical procedure.

¹⁵ Rebecca L. Siegel, MPH, Kimberly D. Miller, MPH & Ahmedin Jemal, DVM, PhD, *Cancer Statistics, 2018*, 68 CA CANCER J. CLIN. 7–30 (2018).

¹⁶ E.A. Mittendorf et al., *Incorporating Biology into Breast Cancer Staging: American Joint Committee on Cancer, Eight Edition, Revisions and Beyond*, ASCO Educational Book 2018; G.N. Hortobagyi et al., *AJCC Cancer Staging Manual: Breast (ed 8)*. New York, NY: Springer International Publishing (2016).

IV. Treatment Development: The Drug Development Life-Cycle

A. Investigational New Drugs – The Phases of Drug Development

In order for a new drug to be approved and commercially available, every pharmaceutical company has to first submit an Investigational New Drug application (IND)¹⁷ and then based on the IND studies submit a marketing authorization application, a New Drug Application (NDA), or in the case of biological drugs, a Biologic Licensing Application (BLA). It is within this framework that the safety and effectiveness of new drugs are first studied.

1. The IND: Preclinical Studies

The IND application provides data on the manufacture of the drug, the preclinical animal studies, *in vitro* studies, and protocols for future studies on human participants.¹⁸ The purpose of the manufacturing information, which characterizes the new drug, and the animal toxicology studies are to help assure that the first clinical trials in humans will be safe. The safety findings in animals, particularly at exaggerated dosing are used to identify the types of adverse experiences which may be observed in clinical trials and later clinical experience.

Determination of the starting dose for the first human studies is also estimated from the preclinical studies. There is an imperfect relationship between the animal dose findings and the safe human dose, so initial human studies start very low and then escalate the dose as safety is established. Preclinical animal species have different drug absorption and metabolism, and drugs may exert their toxicity differently in different species. Although the preclinical toxicity results will be replaced by the more relevant human experience, these studies provide important information on how to design the first-in-human clinical trials that will open the IND.

2. The IND: Phase 1, 2 and 3 Studies

The new drug then is studied in a number of clinical trials to establish safety and effectiveness in humans. IND sponsors closely monitor patients in the IND clinical studies to detect adverse effects. Some adverse effects are predictable by the pharmacology mechanism of action of the drug, but not all adverse effects can be anticipated, so the drug effects across many different body systems are monitored. The studies will determine the new drug dose, schedule of

¹⁷ Requirement for an IND. 21 C.F.R. §312.20.

¹⁸ IND content and format. 21 C.F.R. § 312.23.

administration, safety monitoring, and evidence of effectiveness in the specific patient populations, and conditions where the drug is tested.

Phase 1 trials are small closely monitored studies, often in healthy volunteers, but in cancer drug development, more typically in patients, where the risks of the investigational drug are more appropriately studied where there is potential benefit. In Phase 1 trials the goal is to learn how a drug is absorbed and eliminated from the body and to determine appropriate doses for further testing. Typically, fewer than 100 subjects participate in Phase 1 trials.

To assure the initial doses in humans are safe, the human Phase 1 and 2 studies typically study different doses. Dose selection may aim to identify the minimally effective dose, and for some drugs—cancer drugs in particular—the maximally tolerated dose. Phase 2 trials are used to establish dose, provide proof of concept of efficacy and evaluate the safety and effectiveness of the drug for patients with specific conditions. Phase 2 studies often involve several hundred patients. They are used to learn enough about the drug to plan the larger trials in Phase 3 that will confirm the safety and effectiveness of the drug for one or more indications. Phase 3 trials, depending on the condition, may involve hundreds to several thousand patients.

Evaluation of approved drugs continues after a drug is on the market, which is described below, but at the time of approval the prescribing physician must be able to select patients likely to benefit from the drug, be able to assess safety risks and to be able to make patient-specific and indication-specific drug dosing decisions.

B. Approval for New Drugs

With FDA approval of a sponsor's New Drug Application (NDA) a product can be marketed in the United States. The approval is specific to the manufacturer, pharmaceutical formulation(s) of the drug, and for specific intended uses (indications) where effectiveness was demonstrated by adequate and well controlled studies.

The NDA includes detailed data from the preclinical studies, Phase 1, 2 and 3 trials, as well as postmarketing experience in other countries, when it exists. Generally, the NDA contains the following information: (i) reports of preclinical and clinical studies; (ii) a summary of all safety data; (iii) pharmacological data on the drug's composition; (iv) methods and facilities used in the drug's manufacturing; (v) samples of the product; and (vi) proposed prescribing information.

Once a product is approved, a concise summary of the essential scientific information for the drug is included in Prescribing Information, also referred to as labeling.

C. Marketed Products: Phase 4 and Postmarketing Safety Surveillance

Clinical studies typically continue after product approval. Phase 4 Postmarketing Commitments are studies that the company agrees to conduct after marketing to provide additional information about specific issues that were identified in the NDA review, but that were not necessary for NDA approval.

Other studies may assess new formulations, or new uses of the drug are often developed which require new Phase 2 and Phase 3 controlled trials and often add substantial and robust information to the safety database.

It is the company's ongoing responsibility to assess safety. After approval, the number of patients who take the drug expands from the few hundreds or thousands of patients in the clinical trials to tens of thousands or even millions of patients who are prescribed the drug by their physicians. New sources of information include: new and ongoing trials at the time of approval conducted by the drug manufacturer; clinical trials conducted by independent investigators; case studies of individual patients or a series of patients; studies describing drug interactions; and the spontaneous reporting of adverse events to the company and the FDA.

To conduct postmarketing surveillance, manufacturers have organized systems to detect, assess and follow up on safety issues. Spontaneous postmarketing adverse event reports identify the following: 1) the adverse event(s); 2) possible suspect drug(s); 3) a specific patient; and 4) the source of the report. These reports on adverse events also have a particular focus on reporting serious and unexpected events. Increases in severity of an expected adverse event, or a change in the character of the adverse event, can take a non-serious and expected event into the category of serious and unexpected.

An important purpose of spontaneous reporting systems is to detect a previously unknown potential association between an adverse effect and a drug. If a potential association is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken. Post-marketing surveillance captures the safety of the product as it is used in clinical practice, whether the use is as indicated in the label or not. Safety in the labeling is not restricted to on label use.

D. Hierarchy of Evidence

For the evidence from any given study of medical therapy, results can be ranked in terms of the: (1) strength of the study design; and, (2) strength of the endpoint assessment. Together, ranking

these two features provides an estimate of the overall strength of the evidence.¹⁹ A formal description of the level of evidence provides a uniform framework for the data, leading to specific recommendations.

The various types of study design are described below in descending order of strength:

1. Prospective, randomized, controlled, clinical trials.
2. Prospective, nonrandomized, controlled, clinical trials.
3. Prospective cohort studies
3. Retrospective case series or other observational study designs based on exposure (i.e., to Taxotere) or on outcome (permanent chemotherapy-induced alopecia).
 - i. Consecutive cases.
 - ii. Nonconsecutive cases or other observational study designs (e.g., cohort or case control studies).

E. Criteria for Assessing Causation

There are scientifically valid criteria that have been used to assess causation. In 1965 Bradford Hill concisely described these criteria in evaluating aspects of an association to especially consider before deciding that the most likely interpretation of it is causation.²⁰ The nine criteria to consider include the following:

1. Strength of the association
2. Consistency of the observed association.
3. Specificity of the association
4. Temporality, i.e., the temporal relation of the exposure to the observed event
5. Biological gradient, i.e., one which can reveal a biological gradient, or dose-response curve
6. Plausibility, i.e., if the causation we suspect is biologically plausible.

¹⁹ The Physician Desk Query editorial board of the National Institutes of Health use a formal ranking system of levels of evidence to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy.

²⁰ Hill AB: **The environment and disease: Association or causation?**

Proceed Roy Soc Medicine – London 1965, **58**:295-300.

7. Coherence: should not seriously conflict with the generally known facts of the natural history and biology of the disease
8. Experiment, i.e., occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent?
9. Analogy, i.e., in some circumstances it would be fair to judge by analogy.

As Bradford Hill noted when he proposed these criteria, none of his nine points to consider can bring indisputable evidence for or against the cause and effect hypothesis and none can be required as a *sine qua non*. As noted in his paper, what the criteria can do, with greater or lesser strength, is to help inform the answer to the fundamental question - is there any other way of explaining the set of facts available, is there any other answer equally, or more, likely than cause and effect? In addition, Bradford Hill notes in his address that "No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis."

F. Prescribing Information

Prescription drug product information, or labeling, includes the prescribing information, as well as all of the advertising, promotion, and many educational activities. The prescribing information²¹ describes in detail the essential information about benefits and risk for the approved indications for use, from the clinical pharmacology, clinical trials, and safety from multiple sources, including controlled studies and postmarketing surveillance. Prescribing Information is an important source of scientific information for healthcare professionals in assessing benefits and risks for their patients.

The prescribing information provides physicians with a clear and concise summary of the information necessary for the safe and effective use of the drug. Prescription drug information is written for the healthcare professionals who prescribe drugs and not to consumers. The prescribing information is a summary of the essential scientific information, providing an

²¹ Sometimes it is referred to as the "PI", the "package insert", or the physician labeling.

evidence-based assessment of risk and benefit for specific indications, to assist a prescriber making decisions for individual patients.²²

Postmarketing surveillance will often identify previously unrecognized adverse events or find cases of increased severity of a known adverse event. New safety findings often require changes in the Prescribing Information. FDA's prescribing information requirements [21 CFR 201(c) (6)] state that safety information must be revised to include a warning about a "clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." NDA supplemental applications are required for certain changes to the product's manufacturing, composition, indications for use, and in the safety and effectiveness information provided in the approved prescribing information.²³

There are two types of prescribing information change applications: those which require FDA's prior approval (Prior Approval Supplements, or PAS); or those which may be implemented immediately,²⁴ usually new safety information to strengthen a Warning, Precaution or Adverse events while the application review by FDA is still pending (Changes Being Effected supplements, or CBE).

G. Specific Comments about Treatment Development in Breast Cancer

Most women diagnosed with breast cancer have early stage, ER/PR positive, HER2/neu negative²⁵ operable disease, a good prognosis, a variety of treatment options to consider, and have high survival rates. The overall 5-year survival for Stage 0 is 100%; stage I (local) is 98%; stage II (regional) is 93%, stage III (advanced regional) is 72-85%; and stage IV (distant) is 22-27%. The overall 5- and 10-year relative survival rates for invasive breast cancer are 90% and 83%, respectively. Most cases (62%) are diagnosed at a localized stage (no spread to lymph nodes, nearby structures, or other locations outside the breast), for which the 5-year survival is

²² Food and Drug Administration, Final rule. 21 CFR Parts 201 and 202 [Docket No. 75N-0066], Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs. Federal Register, 1979. 44(124): p. 37434 - 37467.

²³ Supplements and other changes to an approved application. 21 C.F.R. § 314.70, and Procedures for submission of a supplement to an approved application. 21 C.F.R. § 314.71.

²⁴ In the case of some moderate changes in manufacturing, the changes can be implemented 30 days after submission.

²⁵ As none of the initial cases in the MDL had HER2 positive disease, this report will not summarize treatment for HER2 positive disease.

99%. This is overall data, regardless of the treatment that was or was not received. Survival rates have improved over time for both white and black women but remain about 10% lower (in absolute terms) for black women.

The general treatment considerations for patients with early breast cancer includes the treatment of local disease with surgery, radiation therapy or both, and consideration of systemic therapy with chemotherapy, endocrine therapy, biologic therapy or combinations. The consideration and selection of these approaches are based on prognostic and predictive factors, and include tumor histology, clinical and pathological attributes of the tumor, lymph node involvement, ER/PR and HER2/neu status, multi-gene testing, staging, concomitant medical conditions, age and menopausal status. The risks and benefits of the treatment options are discussed between the patient and her physician, and patient preference is a major ingredient of the decision process, particularly when there are multiple available options from which to select.

Surgery

Surgery is an important and essential component for the treatment of patients with early stage breast cancer. For patients with early stages of breast cancer, the treatment usually involves the primary surgical removal of the cancer. Surgical options include lumpectomy (surgical excision to negative margins of the site of cancer), mastectomy (surgical removal of the affected breast) or mastectomy with reconstruction.

The surgical procedure selected depends on tumor characteristics (e.g., size, hormone receptor status, and extent of spread) and patient preference. Several randomized trials have shown that mastectomy is equivalent to breast-conserving treatment in terms of survival for most women with stages I and II breast cancers.

One or more lymph nodes under the arm (axillary) are usually evaluated during surgery to determine whether the tumor has spread beyond the breast. Axillary assessment in clinically node negative disease is usually performed with sentinel node biopsy (SNB). Randomized clinical trials have shown decreased arm and shoulder morbidity (e.g., pain, lymphedema, sensory loss) in patients with breast cancer undergoing SNB compared with patients undergoing standard axillary lymph node dissection. An axillary dissection may be considered in cases of node-positive breast cancer.

Breast reconstruction may be an option for patients, and all patients undergoing breast cancer treatment should be informed about these options as tailored to their individual clinical situation. Patients should be offered the opportunity to discuss their reconstructive options

with a reconstructive plastic surgeon. Women undergoing mastectomy who elect breast reconstruction have several options, including the type of tissue or implant used to restore breast shape. Reconstruction may be performed at the time of mastectomy (also called immediate reconstruction) or as a second procedure (delayed reconstruction), but often requires more than one surgery.

Treatment provided after the primary surgical resection is called adjuvant therapy. In selected cases in which treatment is provided before the primary surgery, for example, in patients in whom the tumor size is large, and chemotherapy has the potential to shrink the tumor to obtain a better surgical result and facilitate better breast preservation, it is called neoadjuvant therapy.

Radiation Therapy

Radiation can be an important component for the treatment of early stage breast cancer. After breast-conserving surgery, radiation can help lower the chance that the cancer will come back in the breast or nearby lymph nodes. Radiation can also lower the chance for recurrence after a mastectomy, especially if the cancer was larger than 5 cm, or if cancer is found in the lymph nodes. If chemotherapy is part of the treatment plan, then radiation is usually given after the chemotherapy has been completed.

Radiation to the breast is recommended for most patients having breast-conserving surgery. For women with early-stage breast cancer (without spread to the skin, chest wall, or distant organs), studies indicate that breast-conserving surgery plus radiation therapy results in long-term outcomes equivalent to, and possibly even better than, mastectomy. Radiation is sometimes recommended after mastectomy in the case of larger tumors or node-involved breast cancers. Radiation therapy, planning and delivery should be individualized and achieve dose homogeneity of the targeted area and spare normal tissues. The radiation treatment fields are determined by the axillary node status. In patients undergoing lumpectomy with surgical axillary staging, the radiation treatment field recommendations include the following:

Four or more positive axillary nodes - Whole-breast radiation, with or without boost to the tumor bed; radiation to the infraclavicular and supraclavicular areas should also be considered.

One to three positive axillary nodes - Whole-breast radiation, with or without boost to the tumor bed; RT to the infraclavicular and supraclavicular areas should also be considered, as should RT to internal mammary nodes.

Negative axillary nodes - radiation to the whole breast, with or without boost to the tumor bed; in selected patients, partial breast radiation may be considered.

In patients undergoing total mastectomy with surgical axillary staging, with or without reconstruction:

Four or more positive axillary nodes - Radiation to the chest wall plus the infraclavicular and supraclavicular areas and consider radiation to internal mammary nodes.

One to three positive axillary nodes - Consider radiation to the chest wall, with or without infraclavicular and supraclavicular nodes and consider radiation to internal mammary nodes.

Negative axillary nodes and tumor >5 cm or positive margins - Consider radiation to the chest wall, with or without infraclavicular and supraclavicular nodes and consider radiation to internal mammary nodes.

Negative axillary nodes, tumor \leq 5 cm, and margins <1 mm - Radiation to the chest wall is recommended

If the tumor is \leq 5 cm and the surgical margins are \geq 1 mm and there are no axillary nodes, no radiation is needed.

Endocrine Therapy

The need for adjuvant systemic therapy is based on the individual risk of relapse and predicted sensitivity to a particular treatment (e.g., ER/PR). The Early Breast Cancer Trialists' Collaborative Group overview analyses of adjuvant chemotherapy and tamoxifen show reductions in the odds of recurrence and death in all age groups for chemotherapy and endocrine therapy.^{26,27} Many factors weigh in to the decision to use systemic adjuvant therapy. These include considering the balance of the risks and benefits, such as the risk for disease recurrence with local therapy alone, the magnitude of benefit from adding adjuvant therapy, the toxicity(ies) of the therapy, and concomitant medical conditions. The decision is a shared process between the patient and her physician.

²⁶ Early Breast Cancer Trialists' Collaborative Group, *Effects of Chemotherapy and Hormonal Therapy for Early Breast Cancer on Recurrence and 15-Year Survival: An Overview of the Randomized Trials*, 365 LANCET 1687-1717 (2005).

²⁷ Early Breast Cancer Trialists' Collaborative Group, *Comparisons Between Different Polychemotherapy Regimens for Early Breast Cancer: Meta-Analyses of Long-Term Outcome Among 100,000 Women in 123 Randomized Trials*, 379 LANCET 432-44 (2012).

Women with early-stage breast cancers who test positive for hormone receptors benefit from treatment with hormone therapy for 5 or more years. Breast cancer is one of the first cancers for which targeted therapies have been used successfully. The association between estrogen and breast cancer has been known for over 100 years. The first targeted therapies in breast cancer were aimed at the hormone receptors (ER, PR) that are present on many breast cancer cells. Targeted approaches with endocrine therapy remain the mainstay of therapy for ER and/or PR positive cancers. Approaches include tamoxifen, aromatase inhibitors, and ovarian suppression therapy or removal of the ovaries. The treatment option selected depends on the menopausal status of the patient and concerns about the adverse event profile with the treatments e.g., thrombosis with tamoxifen, bone loss with aromatase inhibitors.

Tamoxifen has demonstrated a reduction in the risk of recurrence of breast cancer by about 40% and a reduction in the risk of death by about 30%. It is effective in both premenopausal and postmenopausal women and may be used alone or after chemotherapy.²⁸

The aromatase inhibitors have demonstrated a reduction in the risk of recurrence of breast cancer by approximately 20% compared to tamoxifen in postmenopausal women.^{29,30,31,32} Adverse events that can occur acutely include arthralgias, hot flushes, and gynecologic symptoms, and a long-term adverse event is osteoporosis.

Chemotherapy

In selected patients, treatment may also involve chemotherapy (before or after surgery), and as with all other treatment decisions, this involves a discussion between the patient and her physician. Chemotherapy drugs are generally used in combinations, referred to as regimens. In the 1970s and 1980s, chemotherapy, including anthracycline (e.g., doxorubicin) – or cyclophosphamide-based regimens were developed as safe and effective regimens for patients

²⁸ Early Breast Cancer Trialists' Collaborative Group (EBCTG), *Tamoxifen for Early Breast Cancer: An Overview of the Randomized Trials* 351 LANCET 1451-67 (1998).

²⁹ Dowsett, et al., *Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen*. J Clin Oncol, 2010. **28**(3): p. 509-18.

³⁰ Cuzick, et al., *Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial*. Lancet Oncol, 2010. **11**(12): p. 1135-41.

³¹ Goss, et al., *Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17*. J Natl Cancer Inst, 2005. **97**(17): p. 1262-71.

³² Goss, et al., *Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen*. J Clin Oncol, 2008. **26**(12): p. 1948-55.

with breast cancer. In the 1990s, two taxanes, Taxol/paclitaxel, and Taxotere/docetaxel, were FDA approved for treatment of breast cancer. Treatment regimens in breast cancer have continued to evolve over time.

Generally, chemotherapy regimens are initially studied in patients with advanced, inoperable or metastatic disease to achieve shrinkage of the tumor, or stabilization and prolongation of survival. If found to be safe and effective, the regimens are then studied in earlier stages of the disease, to decrease the recurrence of cancer and improve survival. Improvements may be incremental, and the benefits of small changes in improvement need to be balanced by the downsides of potential risks and individualized for the patient and their preferences.

V. Taxotere and Role as an Option in Early Stage Breast Cancer

Taxotere is a semi synthetic derivative of a precursor extracted from the needles of the European Yew tree, *Taxus baccata*. Taxotere's mechanism of action is as a mitotic inhibitor, preventing cell division. The microtubules are the architecture of the cancer cell's skeleton. Taxotere stimulates microtubule growth, which clogs the process necessary for cell division.

Taxotere was FDA approved for the adjuvant treatment of breast cancer on August 18, 2004.³³ The original NDA for Taxotere was approved (accelerated approval) in May 1996 for the treatment of patients with locally advanced or metastatic breast cancer who had progressed during or relapsed after anthracycline-based therapy. Full approval for the initial indication was in 1998.³⁴ Supplemental NDA approvals for Taxotere were subsequently granted for the treatment of locally advanced or metastatic non-small cell lung cancer previously treated with platinum-based chemotherapy (1999), for the treatment in combination with cisplatin for patients with locally advanced or metastatic non-small cell lung cancer not previously receiving chemotherapy (2000) for the treatment in combination with Prednisone for patients with androgen independent (hormone refractory) metastatic prostate cancer, and for the treatment in

³³ FDA, Taxotere Approval Letter (Aug. 18, 2004), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/20-449s029_Taxotere_approv.PDF (last visited Nov. 19, 2018).

³⁴ FDA, Taxotere Approval Letter (June 22, 1998), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/20449_ltr.pdf (last visited Nov. 19, 2018).

combination with fluorouracil and cisplatin for treatment of patients with locally advanced squamous cell cancer of the head and neck.

The 2004 NDA supplement for adjuvant treatment of early stage breast cancer was FDA-approved based on the interim analysis of a single trial, which was a multicenter, open-label randomized trial (TAX 316) in patients with operable, node-positive breast cancer. 1491 patients were randomized to receive Taxotere (T) vs. 5-fluorouracil (F), each in combination with the same regimen of doxorubicin (A) and cyclophosphamide (C).³⁵ The chemotherapy in each arm was administered every 3 weeks for 6 cycles. After the last cycle of chemotherapy, patients on both arms who were ER and/or PR positive received tamoxifen for up to 5 years. Disease free survival was the primary endpoint; survival, toxicity, and evaluation of pathologic and molecular markers for predicting efficacy were secondary endpoints. The primary endpoint of disease-free survival included local and distant recurrences, contralateral breast cancer and deaths from any cause. Safety was to be evaluated using the NCI-Common Toxicity Criteria. An adverse event is defined in the protocol as “any undesirable event associated with the use of a drug, whether or not considered drug related, and includes any side effect, injury, toxicity, or sensitivity reactions. It also includes any undesirable clinical or laboratory change which does not commonly occur in the patient.”³⁶ All adverse events were to be followed until resolution.

Results from a second interim analysis (median follow-up of 55 months) demonstrated that patients on the Taxotere-containing regimen (TAC) had longer disease-free survival than patients on the control arm (FAC). The overall reduction in the risk of relapse was 25.7% (absolute risk difference 7%). The overall survival was longer on the TAC arm, but not statistically significant when adjusted for the interim analysis. Results from the final analysis, with a median follow-up of 124 months, showed the disease-free survival was 62% for the Taxotere-containing arm vs. 55% for the control (absolute risk difference 7%). 10-year survival was 76% for patients on the Taxotere containing arm vs 69% for the control (absolute risk difference 7%).³⁷

In addition to benefits, treatments have risks (side effects)/adverse events (AE). The Office of Human Research Protections defines an adverse event as any unfavorable and unintended sign

³⁵ Miguel Martín et al., *Adjuvant Docetaxel for Node-Positive Breast Cancer*, 352(22) N. ENGL. J. MED. 2302 (2005).

³⁶ 4th Amended TAX 316 Protocol (Mar. 8, 2002), Sanofi_04816552-655 at p. 62 (Sanofi_04816613).

³⁷ John R. Mackey et al., *Adjuvant Docetaxel, Doxorubicin, and Cyclophosphamide in Node-Positive Breast Cancer: 10-Year Follow-Up of the Phase 3 Randomised BCIRG 001 Trial*, 14 LANCET ONCOL. 72 (2013).

(including an abnormal laboratory finding), symptom, or disease having been absent at baseline, or, if present at baseline, appears to worsen and is temporally associated with medical treatment or procedure, regardless of attribution. The FDA [21 CFR312.32] defines an adverse event as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Treatment-emergent AEs are defined as occurring during treatment with the drug.

The frequency of adverse events are defined by incidence and include the following categories: Very common $\geq 10\%$, ≥ 1 in 10; Common (frequent) $\geq 1\%$ and $< 10\%$, ≥ 1 in 100 and < 1 in 10; Uncommon (infrequent) $\geq 0.1\%$ and $< 1\%$, ≥ 1 in 1000 and < 1 in 100; Rare $\geq 0.01\%$ and $< 0.1\%$, ≥ 1 in 10,000 and < 1 in 1000; and Very Rare $< 0.01\%$, < 1 in 10,000.

In the TAX316 clinical trial, in which 744 patients were exposed to TAC and 736 were exposed to FAC, severe treatment-emergent adverse reactions occurred in 36.3% of the patients on the Taxotere containing arm (TAC) vs. 26.6% on control (FAC); dose reductions due to hematologic toxicity occurred in 1% of cycles in patients on the Taxotere containing arm (TAC) vs. 0.1% on control (FAC); discontinuation of treatment due to adverse reactions was 6.0% (fever in the absence of infection and allergy being the most common reasons) on TAC vs. 1.1% on control (FAC).

Women receiving TAC had an increase in anemia, grade ≥ 3 neutropenia, stomatitis, amenorrhea, fever in the absence of infection, hypersensitivity reactions, peripheral edema, neurosensory and skin events compared to those receiving FAC. Women on the TAC arm also had more grade 3 and 4 adverse events, dose reductions, and treatment discontinuations. The most common adverse event in both arms was reversible alopecia, occurring in over 97% of the patients.

By 2004, there were a number of effective, non-Taxotere containing chemotherapy regimens, including, but not limited to, the first cancer treating taxane, Taxol, that were safe and effective for early stage, operable node-positive breast cancer. This is in addition to other targeted therapies against ER/PR (hormone receptors) and subsequently HER2/neu. There is similar efficacy with Taxotere and Taxol, with different safety profiles.³⁸ The estimated 5-year overall survival for a 3-week schedule was 87.3% for Taxotere, and 86.5% for Taxol, and for a weekly schedule, it was 86.2% for Taxotere and 89.7% for Taxol.

³⁸ Joseph A. Sparano et al., *Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer*, 358 N. ENGL. J. MED. 1663-71 (2008).

VI. Early Stage Breast Cancer Treatment Options

The patients in the MDL have invasive early stage breast cancer, and the majority of patients have ER and/or PR positive, HER2 negative breast cancer. All of the initial cases in the MDL have ER/PR positive, HER2 negative breast cancer. The treatment options relevant to these stages and subtypes of breast cancer will be addressed, and focused on Stage I, IIA, IIB, or IIIA (T3N1M0).

Treatment options depend on the subtype and stage of the breast cancer, and well-informed discussions between a physician and her patient about the risks and benefits of the various options, tailored to the subtype and stage of her breast cancer, and patient preferences.

Section IV.G. summarizes specific issues to consider in the development of treatments for early stage breast cancer, and this section will provide further details about the regimens. The cyclophosphamide and/or anthracycline based regimens continue to play an important role in selected situations given their safety profiles. CMF is a reasonable alternative for patients who have underlying conditions such as cardiac disease where there is a desire to avoid doxorubicin or other anthracyclines. AC would be a reasonable consideration for patients with underlying conditions such as neuropathy where there is a desire to avoid taxanes. Comparable regimens to consider are as follows:

CMF: Cyclophosphamide 100 mg/m² PO on days 1-14 + methotrexate 40 mg/m² IV on days 1 and 8 + 5-fluorouracil 600 mg/m² IV on days 1 and 8 every 4 wk for 6 cycles³⁹

CMF: Cyclophosphamide 600 mg/m² IV + methotrexate 40 mg/m² IV + 5-fluorouracil 600 mg/m² IV on day 1 every 3 wk for 8 cycles

AC: Doxorubicin 60 mg/m² IV + cyclophosphamide 600 mg/m² IV on day 1 every 3 wk for 4 cycles⁴⁰

³⁹ Bonadonna, et al., *30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study*. BMJ, 2005. **330**(7485): p. 217.

⁴⁰ Fisher, et al., *Findings from recent National Surgical Adjuvant Breast and Bowel Project adjuvant studies in stage I breast cancer*. J Natl Cancer Inst Monogr, 2001(30): p. 62-6.⁴¹ Early Breast Cancer Trialists' Collaborative Group, *Effects of Chemotherapy and Hormonal Therapy for Early Breast Cancer Recurrence and 15-Year Survival: An Overview of the Randomized Trials*, 365(9472) LANCET 1687-717 (2005).

Over time, additional regimens have been developed, and reasonable regimens to consider are as follows:

FAC: 5-fluorouracil 500 mg/m² IV on days 1 and 8 + doxorubicin 50 mg/m² IV on day 1 + cyclophosphamide 500 mg/m² IV on day 1 every 3 wk for 6 cycles⁴¹

Dose-dense AC-T(Taxol/paclitaxel): Doxorubicin 60 mg/m² IV on day 1 + cyclophosphamide 600 mg/m² IV on day 1 every 2 wk for 4 cycles, followed by Taxol/paclitaxel 175 mg/m² IV 3 hour infusion on day 1 every 2 wk for 4 cycles⁴²

T(Taxotere/docetaxel)C: Docetaxel 75 mg/m² IV on day 1 + cyclophosphamide 600 mg/m² IV on day 1 every 3 wk for 4 cycles⁴³

CEF: Cyclophosphamide 75 mg/m² PO on days 1-14 + epirubicin 60 mg/m² on days 1 and 8 + 5-FU+ 500 mg/m² IV on days 1 and 8 every 4 wk for 6 cycles

AC-T (Taxol/paclitaxel): Doxorubicin 60 mg/m² IV + cyclophosphamide 600 mg/m² IV on day 1 every 3 wk for 4 cycles, followed by Taxol/paclitaxel 80 mg/m² by IV 1 hour infusion weekly for 12 wk⁴⁴

⁴¹ Early Breast Cancer Trialists' Collaborative Group, *Effects of Chemotherapy and Hormonal Therapy for Early Breast Cancer Recurrence and 15-Year Survival: An Overview of the Randomized Trials*, 365(9472) LANCET 1687-717 (2005).

⁴² Marc L. Citron, et al., *Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741*. J Clin Oncol, 2003. **21**(8): p. 1431-9.

⁴³ Steven E. Jones, et al., *Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer*. Ibid.2006. **24**(34): p. 5381-7.J. CLIN ONCOL. 5381-87 (2006).

⁴⁴ Joseph A. Sparano et al., *Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer*, 358 N. ENGL. J. MED. 1663-71 (2008).

FEC-T (Taxol/paclitaxel): 5-Fluorouracil 600 mg/m² IV + epirubicin 90 mg/m² IV + cyclophosphamide 600 mg/m² IV on day 1 every 3 wk for 4 cycles, followed after 3 wks by paclitaxel 100 mg/m² IV weekly for 8 cycles⁴⁵

T(Taxotere/docetaxel) AC: Taxotere/docetaxel 75 mg/m² IV + doxorubicin 500 mg/m² IV + cyclophosphamide 500 mg/m² IV on day 1 every 3 wk for 6 cycles^{46,47}

FEC-T (Taxotere/docetaxel): 5-Fluorouracil 500 mg/m² IV + epirubicin 100 mg/m² IV + cyclophosphamide 500 mg/m² IV on day 1 every 3 wk for 3 cycles, followed by Taxotere/docetaxel 100 mg/m² IV every 3 wk for 3 cycles⁴⁸

The National Comprehensive Cancer Network (NCCN) Guidelines have been a critical resource for physicians and patients for over 25 years, providing evidence-based, consensus-driven Clinical Practice Guidelines (NCCN Guidelines) management.⁴⁹ The NCCN Guidelines detail the sequential management decisions and interventions, with recommendations based on the best evidence available, including data based on clinical trials, which are continuously updated and revised to reflect new data and clinical information. The NCCN Guidelines provide guidance to physicians for their clinical decision process, with summary data and clinical information supporting recommendations in the algorithms. The NCCN Guidelines note that the best management for any cancer patient is in a clinical trial, and that participation in clinical trials is especially encouraged. Critically important, however, is that the Guidelines do not supplant the physician-patient discussion that must take place, which takes into consideration the risks as well as the benefits of the treatment options, tailored to the subtype and stage of the breast cancer, and taking into account patient preferences.

⁴⁵ Miguel Martin, et al., *Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by Paclitaxel for early breast cancer*. J Natl Cancer Inst, 2008. **100**(11): p. 805-14.⁴⁶ Miguel Martin, et al., *Adjuvant docetaxel for node-positive breast cancer*. N Engl J Med, 2005. **352**(22): p. 2302-13.

⁴⁶ Miguel Martin, et al., *Adjuvant docetaxel for node-positive breast cancer*. N Engl J Med, 2005. **352**(22): p. 2302-13.

⁴⁷ Sandra M. Swain, et al., *Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer*. Ibid.2010. **362**: p. 2053-65.N. ENGL. J. MED. 2053-65 (2010).

⁴⁸ Henri Roche, et al., *Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial*. J Clin Oncol, 2006. **24**(36): p. 5664-71.⁴⁹ NCCN Guidelines, available at <https://www.nccn.org/professionals/default.aspx> (last visit October 2018).

⁴⁹ NCCN Guidelines, available at <https://www.nccn.org/professionals/default.aspx> (last visit October 2018).

Some of the commonly used chemotherapy regimens recommended by NCCN Guidelines over the years for early stage breast cancer have included the following:

- CMF: Cytosan (cyclophosphamide), methotrexate and 5-fluorouracil
- FAC (or CAF): 5-fluorouracil, Adriamycin (doxorubicin), cyclophosphamide
- AC (or CA): Adriamycin (doxorubicin) and Cytosan (cyclophosphamide)
- AC-Taxol: AC followed by Taxol (paclitaxel)
- TAC: Taxotere (docetaxel), Adriamycin (doxorubicin), and Cytosan (cyclophosphamide)
- FEC: 5-fluorouracil, epirubicin and Cytosan (cyclophosphamide)
- AT: Adriamycin (doxorubicin) and Taxotere (docetaxel)
- TC: Taxotere (docetaxel) and Cytosan (cyclophosphamide)

In the January 2008 Version 2 NCCN Guidelines⁵⁰ for early stage breast cancer, the recommended regimens included:

- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide) or FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- AC (doxorubicin/cyclophosphamide) +/- sequential paclitaxel
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide) with filgrastim support
- A→CMF (doxorubicin followed by cyclophosphamide/methotrexate/fluorouracil)
- E→CMF (epirubicin followed by cyclophosphamide/methotrexate/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC x 4 (doxorubicin/cyclophosphamide) + sequential paclitaxel x 4, every 2 weekly regimen with filgrastim support
- A→T→C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every 2 weekly regimen with filgrastim support
- FEC→T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel)
- TC (docetaxel and cyclophosphamide)

Representative regimens with dosing and frequency of administration are provided in the NCCN Guidelines. As noted in the Guidelines, the selection, dosing and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities, individual patient variability, prior treatment, and/or comorbidity. The

⁵⁰ NCCN Guidelines, accessed October 2018

therapeutic options for patients are complex and varied, and the patient and physician have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. Although the treatment Guidelines are frequently based on results of past and present clinical trials, the Guidelines note that there is not a single clinical situation in which the treatment of breast cancer has been optimized with respect to either maximizing cure or minimizing toxicity and disfigurement. With that context, patient/physician participation in prospective clinical trials allows patients to not only receive state-of-the-art cancer treatment but also to contribute to improving the treatment of future patients.

As an example of a clinical trial available during the 2008 timeframe, the National Surgical Adjuvant Breast and Bowel Project (NSABP), an NCI-funded clinical trials cooperative group, was sponsoring a clinical trial NSABP B40⁵¹ for women with palpable and operable HER2 negative breast cancer diagnosed by core needle biopsy. NSABP B40 was a prospective, randomized phase 3 trial evaluating three neoadjuvant docetaxel-based chemotherapy regimens given with or without bevacizumab. The primary aims were (1) to determine whether the addition of capecitabine or gemcitabine to docetaxel followed by AC would increase the rate of complete response as determined by pathology (pCR) in the breast and (2) to determine whether the addition of bevacizumab to the docetaxel/anthracycline based regimens would increase the rate of pCR relative to the same docetaxel/anthracycline-based regimens without bevacizumab.

In the 2018 Version 3 NCCN Guidelines⁵² for early stage breast cancer, the recommended regimens include many of the regimens recommended in earlier versions of the NCCN Guidelines. It is important to note that the side effect profile, even with effective regimens, plays a substantial role in determining the appropriate regimens to consider, and is a component of the rationale for the importance of the risk-benefit discussion between the patient and her physician. The 2018 NCCN recommendations on treatment of early stage breast cancer are as follows:

⁵¹ http://www.nsabp.pitt.edu/B40_Protocol_Brochure.pdf Accessed October 2019.

⁵² NCCN Guidelines, accessed October 2018, and includes the guidelines for breast cancer dated October 25, 2018.

Dose-dense AC-T (Taxol/paclitaxel every 2 weeks): Doxorubicin 60 mg/m² IV day 1 + cyclophosphamide 600 mg/m² IV day 1 every 14 days for 4 cycles, followed by Taxol/paclitaxel 175 mg/m² by IV 3-hour infusion day 1 every 14 days for 4 cycles⁵³

Dose-dense AC-T (Taxol/paclitaxel weekly): Doxorubicin 60 mg/m² IV day 1 + cyclophosphamide 600 mg/m² IV day 1 every 14 days for 4 cycles, followed by Taxol/paclitaxel 80 mg/m² by IV 1-hour infusion weekly for 12 weeks

Taxotere(docetaxel) + C: Taxotere/docetaxel 75 mg/m² IV day 1 + cyclophosphamide 600 mg/m² IV day 1 every 21 days for 4 cycles⁵⁴

AC-T (Taxotere/docetaxel every 3 weeks): Doxorubicin 60 mg/m² IV on day 1 + cyclophosphamide 600 mg/m² IV day 1, every 21 days x 4 cycles, followed by Taxotere/docetaxel 100 mg/m² IV on day 1, every 21 days for 4 cycles⁵⁵

EC: Epirubicin 100 mg/m² IV day 1 + cyclophosphamide 830 mg/m² IV day 1, every 21 days for 8 cycles⁵⁶

⁵³ Marc L. Citron, et al., *Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741*. J Clin Oncol, 2003. **21**(8): p. 1431-9.⁵⁴ Steven Jones et al., *Docetaxel with Cyclophosphamide Is Associated with an Overall Survival Benefit Compared with Doxorubicin and Cyclophosphamide: 7 Year Follow-up of U.S. Oncology Research Trial 9735*, 27 J. CLIN. ONCOL. 1177-83 (2009).

⁵⁴ Steven Jones et al., *Docetaxel with Cyclophosphamide Is Associated with an Overall Survival Benefit Compared with Doxorubicin and Cyclophosphamide: 7 Year Follow-up of U.S. Oncology Research Trial 9735*, 27 J. CLIN. ONCOL. 1177-83 (2009).

⁵⁵ G. von Minckwitz et al., *Doxorubicin with Cyclophosphamide Followed by Docetaxel Every 21 Days Compared with Doxorubicin and Docetaxel Every 14 Days as Preoperative Treatment in Operable Breast Cancer: The GEPAR DUO Study of the German Breast Group*, 23(12) J. CLIN. ONCOL. 2676-85 (2005).

⁵⁶ M.J. Piccart et al., *Phase III Trial Comparing Two Dose Levels of Epirubicin Combined with Cyclophosphamide with Cyclophosphamide, Methotrexate and Fluorouracil in Node-Positive Breast Cancer*, 19 J. CLIN. ONCOL. 3103-10 (2001).

T (Taxotere/docetaxel) AC: Taxotere/docetaxel 75 mg/m² IV day 1 + doxorubicin 50 mg/m² IV day 1 + cyclophosphamide 500 mg/m² IV day 1 every 21 days for 6 cycles⁵⁷

Dose dense AC: Doxorubicin 60 mg/m² IV day 1 + cyclophosphamide 600 mg/m² IV day 1 every 14 days for 4 cycles

AC (every 3 weeks): Doxorubicin 60 mg/m² IV day 1 + cyclophosphamide 600 mg/m² IV day 1 every 21 days for 4 cycles⁵⁸

CMF: Cyclophosphamide 100 mg/m² po days 1-14 + methotrexate 40 mg/m² IV days 1 and 8 + 5-fluorouracil 600 mg/m² IV days 1 and 8, every 28 days for 6 cycles⁵⁹

AC -T (Taxol/paclitaxel weekly): Doxorubicin 60 mg/m² IV day 1 + cyclophosphamide 600 mg/m² IV day 1 every 21 days for 4 cycles, followed by Taxol/paclitaxel 80 mg/m² by IV 1-hour infusion weekly for 12 weeks⁶⁰

Patients may have concomitant medical conditions that may require consideration of treatment options that do not have the potential to exacerbate the underlying condition. For example, patients may have pre-existing cardiac disease or neuropathy, and want to mitigate or avoid the use of specific therapies, such as anthracyclines and taxanes. For patients with significant concomitant conditions, such as congestive heart failure, chronic obstructive pulmonary disease, cirrhosis, or chronic renal insufficiency, the prognosis for the concomitant condition

⁵⁷ Miguel Martin, et al., *Adjuvant docetaxel for node-positive breast cancer*. N Engl J Med, 2005. **352**(22): p. 2302-13.

⁵⁸ Fisher et al., *Two Months of Doxorubicin-Cyclophosphamide with and Without Interval Reinduction Therapy Compared with 6 Months of Cyclophosphamide, Methotrexate, and Fluorouracil in Positive-Node Breast Cancer Patients with Tamoxifen-Nonresponsive Tumors: Results from the National Surgical Adjuvant Breast and Bowel Project B-15*, 8 J. CLIN. ONCOL. 1483-96 (1990).⁵⁹ Goldhirsch et al., *Adding Adjuvant CMF Chemotherapy to Either Radiotherapy or Tamoxifen: Are All CMFs Alike? The International Breast Cancer Study Group (IBCSG)*, 9 ANN. ONCOL. 489-93 (1998).

⁵⁹ Goldhirsch et al., *Adding Adjuvant CMF Chemotherapy to Either Radiotherapy or Tamoxifen: Are All CMFs Alike? The International Breast Cancer Study Group (IBCSG)*, 9 ANN. ONCOL. 489-93 (1998).

⁶⁰ Joseph A. Sparano et al., *Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer*, 358 N. ENGL. J. MED. 1663-71 (2008).

should be considered in the context of the cancer.⁶¹ The physician would take these concomitant conditions into account, if they exist, as well as patient preferences, in a discussion of the benefit-risk of treatment options for their patients.

It has been known for years that most patients with early stage breast cancer, especially stages I and II, have a good prognosis, and that many would not benefit from chemotherapy either in delaying breast cancer recurrence or improving survival. Until the recent development of genetic tests assessing the risk of recurrence, starting in 2005, and trials that have helped guide which patients do or do not benefit, doctors reviewed the risks and benefits of chemotherapy, biologic therapy and hormone therapy options with their patients and made treatment plans together based on patient acceptance of toxicities for a potential small incremental benefit in reducing their individual recurrence risk.

Recently published clinical trial results from TAILORx⁶², with 9 years of follow-up, show genetic testing of the tumor in patients with early stage breast cancer who are ER/PR positive, HER2/neu negative, node negative, to determine who benefits from chemotherapy is changing the landscape of therapy tailored to the patient. Up to 85% of women (those with low to intermediate risk of recurrence shown by genetic testing of their tumors) showed no added benefit of chemotherapy compared to endocrine therapy alone. The ongoing clinical trial RxPONDER is assessing the role of chemotherapy with genetic testing for risk of recurrence in ER/PR positive, HER2/neu negative, node positive breast cancer, and assessing whether chemotherapy provides any benefit to endocrine therapy alone for those with intermediate risk of recurrence.

VII. The Role of the Physician and Patient in Choosing Treatment Options

A. Informed Consent, Well-Informed of Complete Information about Risks

Management of breast cancer is based on an informed discussion between the patient and her physician, and the treatment selected is based on the benefits and risks of the intervention,

⁶¹ M.E. Charleson et al., *A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation*, 40(5) J. CHRONIC DIS. 373-83 (1987).

⁶² Joseph A. Sparano, MD et al., *Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer*, 379 N. ENGL. J. MED. 111-21 (2018).

tailored to the stage and characteristics of the tumor and medical conditions of the patient, taking into account patient preferences. The ultimate choice regarding treatment belongs to the patient. A patient with breast cancer needs information from her physician on the effectiveness and safety (e.g., adverse events) of the various treatment options relevant for her breast cancer. In addition, patients may discuss treatment options with friends, family, colleagues, and other health care providers, but ultimately, it's the discussion between a patient and her physician about the benefits and risks of her treatment options. Some of the most important possible adverse events are those that can potentially be life threatening; cause permanent damage (e.g., irreversible disfiguring or irreversible morbidities), or are otherwise important to patient priorities.

Physicians learn from many sources of information about treatment options, enabling an informed discussion with their patient about her treatment options. These sources include prescribing information, scientific and medical publications; presentations and publications of clinical trials; professional meetings; their own experience as well as colleagues; NCCN Guidelines; other Guidelines, including ASCO; and company sources such as labeling, promotional material⁶³, advertising, and sales representatives.

VIII. Taxotere and Alopecia

Alopecia is defined as partial or complete absence of hair from any area of the body where it normally grows.

A. Chemotherapy-induced Transient and Reversible Alopecia

Chemotherapy-induced transient and reversible alopecia (CIA) is a known, very common adverse event in breast cancer. CIA is most prominent on the scalp in areas with low total hair densities, in particular the crown and frontal areas of the scalp, where there is also slower hair recovery. Total scalp alopecia is common, but hair loss can be diffuse or patchy. Loss of eyebrows and eyelashes may also occur. Common chemotherapy drugs, at standard doses and schedules in breast cancer known to cause CIA include the anthracyclines (doxorubicin, epirubicin), cyclophosphamide, and taxanes.

In the transient and reversible CIA, most hair loss starts within 2 weeks of the first cycle of chemotherapy, and hair may be completely lost by the end of the second cycle of chemotherapy.

⁶³ Prescribing information labeling, initial Launch advertising, and Direct-to-Consumer material is pre-approved by FDA.

Hair grows back within 3 to 6 months of the end of chemotherapy. The regrown hair may be different from the patient's hair before chemotherapy, in color, texture, or shape (straight or curly).

The transient/reversible hair loss due to cytotoxic chemotherapy is due to the chemotherapy attacking rapidly dividing cells, including the dividing hair matrix cells. The hair loss occurs by either of two mechanisms: 1) temporary damage to the hair follicle matrix keratinocytes during the active growth phase (anagen) of the hair cycle and/or 2) thinning of the hair shaft, resulting in breakage during the resting phase (telogen) of the hair cycle.

In the TAX 316 study, alopecia during treatment occurred in 97.8% of patients on Taxotere-containing arm (TAC) vs. 97.1% on control (FAC).⁶⁴ Alopecia remained present 31 days after the last chemotherapy in 92.3% for patients on the Taxotere-containing arm (TAC) vs. 87.6% on control (FAC).⁶⁵

B. Chemotherapy-Induced Permanent, Irreversible Alopecia

Permanent, irreversible hair loss due to chemotherapy (PCIA) has been defined as an absence of or incomplete hair regrowth 6 months beyond completion of chemotherapy.⁶⁶ PCIA is thought to be likely a result of the hair follicle being permanently damaged, and the hair density is markedly reduced. It has been hypothesized that this may be due to irreversible damage of the stem cells/hair matrix cells of the hair bulb, or disturbance of the signaling pathways to the secondary hair germ.⁶⁷ Prior to the experience with Taxotere in breast cancer patients, PCIA was primarily seen in patients receiving high doses of selected chemotherapy agents in the

⁶⁴ TAX 316 Clinical Study Report (Sept. 9, 2010) at p. 37, Sanofi_02645236.

⁶⁵ *Id.* at p. 69, Sanofi_02645268.

⁶⁶ Ben Tallon, MBChC et al., *Permanent Chemotherapy-Induced Alopecia: Case Report and Review of the Literature*, 63(2) J. AM. ACAD. DERMATOL. 333-36 (2010).

⁶⁷ See, e.g., *id.* and Christos Prevezas et al., *Irreversible and Severe Alopecia Following Docetaxel or Paclitaxel Cytotoxic Therapy for Breast Cancer*, 160 BRIT. J. DERMATOL. 881 (2009).

transplant setting.⁶⁸ it was not a recognized adverse event using standard doses of chemotherapy in cancer patients.⁶⁹

In the randomized studies with Taxotere in breast cancer the following adverse events with alopecia were shown:

In TAX 316 (node positive breast cancer) 92.3% of patients on the Taxotere-containing regimen (TAC) and 87.6% of patients on control (FAC), had alopecia at 31 days after the last cycle of chemotherapy.⁷⁰ At the end of the 10-year follow up period, PCIA was seen in 3.9% (n=29) of patients on the Taxotere-containing regimen (TAC) and in 2.2% (n=16) on the control (FAC).⁷¹

In GEICAM 9805, with the identical treatment regimens as in TAX316, but in node negative breast cancer, 96.6% on the Taxotere containing regimen (TAC) and 97.9% on the control arm (FAC) had alopecia during treatment;⁷² however, only 9.2% (rather than the 92.3% and 87.6% as noted on TAX 316) of patients were followed for alopecia 31 days after the last cycle of chemotherapy; at 77 months, even with this very low % of follow-up of 84 patients, 3 of the 49 patients on TAC had ongoing PCIA, with 1 of 35 patients on FAC.⁷³

It is not a good practice to fail to follow the adverse event of alopecia into the follow-up period in a clinical trial, particularly when duration and severity of the alopecia suggests the need for further investigation. In clinical trials, collection of adverse event information begins at the initiation of study drug, and the adverse events should be followed to resolution or stabilization. Follow-up for adverse events that result in drug discontinuation, or for studies in

⁶⁸ See, e.g., M.E. de Jonge et al., *Relationship Between Irreversible Alopecia and Exposure to Cyclophosphamide, Thiotepa and Carboplatin (CTC) in High-Dose Chemotherapy*, 30 BONE MARROW TRANSPLANTATION 593-97 (2002); Antonella Tosti, MD et al., *Permanent Alopecia After Busulfan Chemotherapy*, 152 BRIT. J. DERMATOL. 1056-58 (2005).

⁶⁹ Ben Tallon, MBChC et al., *Permanent Chemotherapy-Induced Alopecia: Case Report and Review of the Literature*, 63(2) J. AM. ACAD. DERMATOL. 333-36 (2010).

⁷⁰ TAX 316 Clinical Study Report (Sept. 9, 2010) at p. 69, Sanofi_02645268.

⁷¹ *Id.* at p. 37, Sanofi_02645236.

⁷² Miguel Martín, MD, PhD et al., *Adjuvant Docetaxel for High-Risk, Node-Negative Breast Cancer*, 363(23) N. ENGL. J. MED. 2200, 2208 (2010).

⁷³ GEICAM 9805 Clinical Study Report (Nov. 9, 2009) at 111, Sanofi_01061868.

which the adverse events are present at the end of study treatment is also done. Documentation of the adverse event should include the following:

Date the adverse event began; treatment for the adverse event (e.g., no treatment needed, further testing to diagnose the event, hospitalization, dose reduction, holding of a study intervention); description of the event in enough detail that a CTCAE⁷⁴ term and grade can be assigned as part of data management activities; attribution of the adverse event; date the adverse event resolved; if an ongoing adverse event worsens or improves in its severity or its relationship to the study drug changes, documentation should be collected.

In a published survey of patient perspectives on transient reversible chemotherapy-induced alopecia, 47% of female patients consider hair loss the most traumatic aspect of chemotherapy and 8% would decline chemotherapy because of fear of hair loss.⁷⁵ The perspectives on permanent, not just transient and reversible, alopecia might be anticipated to be higher.

Multiple abstracts, publications and reports after FDA approval of Taxotere have noted PCIA, starting in 2001 and extending into 2019. Postmarketing surveillance has demonstrated PCIA as a Taxotere adverse event. The cases of PCIA started in 2001 and continue into 2019, and are listed in Table 2, as well as briefly described in the narratives below:

The two company-sponsored randomized clinical trials with Taxotere/docetaxel in early stage breast cancer patients show the increased risk of PCIA. There are no reports from randomized clinical trials with non-Taxotere/docetaxel conventional chemotherapy in early stage breast cancer showing an increased incidence of permanent chemotherapy-induced alopecia.

The following issues were considered in evaluating the various studies:

1. How were the patients selected?
 - by treatment (or even ‘for’ treatment in a clinical trial) – these studies look prospectively for outcomes (even when done retrospectively with a chart review of previously treated patients.) Experimental studies are called clinical trials, observational studies are exposure cohort studies: patients treated, not in a study but as part of medical practice, treatment registries

⁷⁴ U.S. Dept. of Health and Human Services, *Common Terminology Criteria for Adverse Events (CTCAE): Version 5.0* (Nov. 27, 2017).

⁷⁵ Ralph M. Trüeb, *Chemotherapy-Induced Alopecia*, 4(4) CURR. OPIN. SUPPORT. PALLIAT. CARE 281-84 (2010).

- by outcome, i.e., permanent, persistent or irreversible chemotherapy induced alopecia – these studies look back at treatments that could have caused the alopecia – these are case studies, not clinical trials, that look back from the outcome to identify risk factors for that outcome. Although the studies may include interaction with patients, it is not a clinical trial of a treatment. All outcome studies are observational as outcomes, because unlike treatments, the outcome cannot be experimentally assigned.

2. Was there a control group?

- Treatment trials can have a randomized control group, or nonrandomized control groups, or no control at all as is done with a consecutive series of treated patients
- Outcome studies can have a control group (the case-control study design) which can be randomly sampled from control populations

3. Was data collected prospectively or retrospectively?

- Outcome studies are inherently retrospective with respect to causation even when there is contact with patients and ongoing follow-up from that point.
- Treatment studies are inherently prospective from the time of treatment, but the information may be gathered retrospectively on historical patients.

4. How did the study control for bias?

- In selection of patients: randomization in trials, in consecutive series or less commonly sampling in outcome studies
- Was there direct collection of data from patients or just from medical records. Was there a protocol and case report form (CRF)? (With pharmacovigilance the information is more limited since only the reporter of the event can be queried by the company)
- In the classification of outcomes, blinding of the assessment of outcomes to treatment (the double or triple blind RCT, the blinded adjudicator in observational studies); in the completeness of patient selection and follow-up (missing data, missing patients, missing information in CRFs and gaps in medical records)

- Did they control covariates? Did they control for multiplicity (i.e., did they look at many outcomes or was this a study focused on one in particular)?

C. Table 2 – Publications⁷⁶ on PCIA in the Treatment of Breast Cancer⁷⁷

Reference	Taxotere/ docetaxel Regimen	Taxol/ paclitaxel Regimen	Taxotere + Taxol Regimen	Taxane (not specified) Regimen	Non- taxane Regimen	Type of Study ⁷⁸	Bradford-Hill Criteria
TAX 316	29				16	1a. (paper) Randomized controlled clinical trial	-strength of association -consistency

⁷⁶ I conducted a comprehensive search using PubMed as well as End Note using the terms permanent, irreversible or persistent alopecia, breast cancer, chemotherapy or chemically-induced, as well as terms for the chemotherapy commonly used in early stage breast cancer – i.e., taxanes (taxotere or docetaxel, taxol or paclitaxel), anthracyclines (doxorubicin, Adriamycin), cyclophosphamide (cytoxan), methotrexate and 5-fluorouracil. In addition, I specifically searched for the additional chemotherapies also used in the NSABP B40 clinical study, gemcitabine and bevacizumab. See summary at end of Table 2 regarding results of search for persistent, permanent or irreversible alopecia and gemcitabine and bevacizumab. The paper must have attribution of the chemotherapy used, the numbers of patients on each of the regimens, and whether persistent, permanent or irreversible alopecia is evaluated.

⁷⁷ At the end of the 10-year follow up period for TAX 316, PCIA was seen in 3.9% (n=29) of patients on the Taxotere-containing regimen (TAC) and in 2.2% (n=16) on the control (FAC). These numbers are not included in the published studies: Miguel Martín et al., *Adjuvant Docetaxel for Node-Positive Breast Cancer*, 352(22) NEW ENGL. J. MED. 2302 (2005); John R. Mackey et al., *Adjuvant Docetaxel, Doxorubicin, and Cyclophosphamide in Node-Positive Breast Cancer: 10-Year Follow-Up of the Phase 3 Randomised BCIRG 001 Trial*, 14 LANCET ONCOL. 72 (2013). The PCIA numbers are included in the Clinical Study Report. TAX 316 Clinical Study Report (Sept. 9, 2010) at p. 69, Sanofi_02645268.

⁷⁷ Only 9.2% (rather than the 92.3% and 87.6% as noted on TAX 316) of patients were followed for alopecia 31 days after the last cycle of chemotherapy in GEICAM 9805; at 77 months, even with this very low % of follow-up of 84 patients, 3 of the 49 patients on TAC had ongoing PCIA, with 1 of 35 patients on FAC. These numbers were not included in the published study Miguel Martín, MD, PhD et al., *Adjuvant Docetaxel for High-Risk, Node-Negative Breast Cancer*, 363(23) N. Engl. J. Med. 2200, 2208 (2010). The PCIA numbers are included in the Clinical Study Report GEICAM 9805 Clinical Study Report (Nov. 9, 2009) at 111, Sanofi_01061868.

⁷⁸ 1. Prospective studies: 1a randomized controlled clinical trials; 1b non-randomized, controlled clinical trials; 1c prospective cohort or case series
2. Retrospective studies: 2a. consecutive series; 2b. case series or individual case reports

							-specificity -temporality -plausibility -coherence -experiment
GEICAM 9805	3				1	1a. (paper) Randomized controlled clinical trial	-strength of association -consistency -specificity -temporality -plausibility -coherence -experiment
Total	32				17		
There are no randomized clinical trials of non-Taxotere/docetaxel given in standard doses for early stage breast cancer that show an increased risk for permanent chemotherapy-induced alopecia. The incidence of PCIA in the Taxotere-based regimen is almost double the incidence of PCIA in the control arm (each arm of this randomized clinical trial contained the identical AC regimen, so that the contribution of Taxotere could be isolated)							
Nabholtz (2001) ⁷⁹	4					1b. (paper) Prospective clinical trial of breast cancer patients treated with taxotere regimen, with alopecia graded	-temporality -plausibility -coherence

⁷⁹ J.M. Nabholz et al., *Phase II Study of Docetaxel, Doxorubicin, and Cyclophosphamide as First-Line Chemotherapy for Metastatic Breast Cancer*, 19(2) J. CLIN. ONCOL. 314-21 (2001).

						according to standard criteria (NCI CTC) and monitored at regular intervals with median follow of 32 months	
Bertrand (2013) ⁸⁰	26					1b. (abstract) Prospective non-randomized clinical trial of scalp cooling during chemotherapy to prevent permanent alopecia in breast cancer patients who received taxotere chemotherapy and evaluated for risk factors in patients who still developed PCIA vs those who did not.	-temporality -plausibility -coherence

⁸⁰ M. Bertrand et al., *Permanent Chemotherapy Induced Alopecia in Early Breast Cancer Patients After (Neo)adjuvant Chemotherapy: Long Term Follow Up*, Abstract P3-09-15 at 36th Annual San Antonio Breast Cancer Symposium (2013).

Kang (2018) ^{81,82}	23				3	1c. (paper) Prospective cohort study in non-randomized, consecutive series of patients with early stage breast cancer expected to receive adjuvant chemotherapy at the outpatient breast cancer clinic in Seoul, Korea. The objective of the study was to estimate the long-term incidence of PCIA in a cohort of patients with breast cancer whose hair volume and density were measured	-consistency -specificity -plausibility -coherence
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⁸¹ Personal communication with author Kang on October 2, 2018: The 2017 Kang et al. abstract CS11-4 at the World Congress for Hair Research had incorrectly stated the drug as paclitaxel, rather than the drug that was actually administered, Taxotere. The author requested the abstract to be corrected, but this was not done before publication of the abstract book. The article, published on the same study by the same author in 2018, correctly provided the attribution to Taxotere.

⁸² Danbee Kang et al., *Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study*, 23 THE ONCOLOGIST 1-7 (2018).

						prior to chemotherapy and who were followed for 3 years after chemotherapy.	
Martin (2018) ⁸³	36					2a. (paper) Retrospective evaluation across 3 institutions in Spain of the prevalence of PCIA in breast cancer patients with consecutively treated non-randomized adjuvant treatment with 8 years of follow-up	-specificity -consistency -temporality -plausibility -dose response
Kim (2017) ^{84,85}				93	29	2a.(paper) Cross-sectional survey retrospectively identified breast cancer patients who had non-	-consistency -specificity -temporality -plausibility -coherence

⁸³ Miguel Martín et al., *Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling*, 171(3) BREAST CANCER RES. TREAT. 627-34 (2018).

⁸⁴ Personal communication with senior author Sohn on October 2, 2018: The authors did not collect nor analyze by type of taxane regimen, so there can be no attribution.

⁸⁵ Gun Min Kim et al., *Chemotherapy-Induced Irreversible Alopecia in Early Breast Cancer Patients*, 163 BREAST CANCER RES. TREAT. 527-33 (2017).

						randomly received doxorubicin, cyclophosphamide alone or followed by a taxane as neoadjuvant or adjuvant chemotherapy. A prospective questionnaire regarding alopecia as well as the measurement of hair density was conducted.	
Bourgeois (2010) ⁸⁶	104				4	2a. (3 abstracts) Retrospective comparative review of breast cancer patients who had been treated (non-randomized) in 15 institutions across France with adjuvant chemotherapy over a 2 year time frame, with a minimum of at least 6	-specificity -consistency -temporality -plausibility -coherence

⁸⁶ H. Bourgeois, *Long Term Persistent Alopecia and Suboptimal hair regrowth after adjuvant chemotherapy for Breast Cancer*. 2009. *Long Term Persistent Alopecia and Suboptimal Hair Regrowth after Adjuvant Chemotherapy for Breast Cancer: Alert for Emerging Side Effect: French ALOPERS Observatory*, 21(8) ANNALS OF ONCOL. Viii83-84 (2010).

						months since completion of adjuvant chemotherapy and an updated median time of follow-up of 3.7 years . Prospectively designed case report forms and questionnaire to assess for permanent alopecia	
Sedlacek (2006) ⁸⁷	7					2a. (abstract) Retrospective comparative non-randomized review of prospectively consecutively treated breast cancer patients at the physician's institution with at least 1 year of follow-up post conclusion of adjuvant chemotherapy with either a taxotere,	-consistency -specificity -temporality -plausibility -coherence

⁸⁷ S.M. Sedlacek, *Persistent Significant Alopecia (PSA) from Adjuvant Docetaxel After Doxorubicin/Cyclophosphamide (AC) Chemotherapy in Women with Breast Cancer*, 100 BREAST CANCER RES. TREAT. s116 (2006).

						paclitaxel, or non-taxane regimen	
Crown (2017) ⁸⁸ , and Crown (2017) ⁸⁹	40	3			1	2a. (abstracts) Retrospective study: A prospectively designed telephone interview survey (approved by the Hospital audit committee) was conducted of early stage breast cancer patients recorded in their database who had completed adjuvant or neo-adjuvant anthracycline and/or taxane-based chemotherapy on clinical trials more than 1 year earlier and assessed as to the number and severity of	-consistency -temporality -plausibility -dose-response -coherence

⁸⁸ Crown et al., *Incidence of permanent alopecia following adjuvant chemotherapy in women with early stage breast cancer*, Journal of Clinical Oncology 35, no. 15 supplement e21576, (2017).

⁸⁹ Crown et al., *Incidence of Permanent alopecia following adjuvant chemotherapy in women with early stage breast cancer*, poster number 205-P, 2017

						ongoing alopecia. The study also evaluated the relationship of docetaxel dose to the number and severity of ongoing alopecia.	
Thorp (2015) ⁹⁰	21					2a. (abstract) Retrospective evaluation of early stage breast cancer patients treated with taxotere/docetaxel-regimens and completed their treatment at least 3 years earlier at their regional cancer center using a prospectively designed questionnaire to determine the incidence, site, extent	-temporality -plausibility -coherence

⁹⁰ Nicola J. Thorp, *Long Term hair loss in patients with early breast cancer receiving docetaxel chemotherapy*. May 1. 2015. p. Sanofi_002785 to Sanofi_002788. (2015).

						and duration of hair loss.	
Freites-Martinez (2019) ⁹¹	31 (25) if take into account 81% were breast cancer patients	47 (38) if take into account 81% were breast cancer patients	2		18 (15) if take into account 81% were breast cancer patients	2b. (paper) Retrospective, multicenter non- randomized case study and patients were eligible if they received only systemic cytotoxic chemotherapy with a clinical diagnosis of PCIA or received chemotherapy followed by endocrine therapies but the alopecia was associated with endocrine therapy.	-temporality -specificity -plausibility
Kluger (2012) ⁹²	19		1			2b. (paper). Retrospective case	-temporality -plausibility

⁹¹ Azael Freites-Martinez, MD et al., Assessment of Quality of Life and Treatment Outcomes of Patients with Persistent Postchemotherapy Alopecia, JAMA Dermatol, published online March 6, 2019. Of note, only 81% of the 98 patients were breast cancer patients, and in this category, only 75 of the 98 patients had clinical characteristics of the alopecia noted, only 45 of the 98 had trichoscopy performed, and only 41 of 98 had data on quality of life. The proportions of patients who had breast cancer, and the type of regimen received in these subsets, was not provided.

⁹² Nicolas Kluger et al., *Permanent Scalp Alopecia Related to Breast Cancer Chemotherapy by Sequential Fluorouracil/Epirubicin/Cyclophosphamide (FEC) and Docetaxel: A Prospective Study of 20 Patients*, 23 ANNALS OF ONCOL. 2879 (2012).

						studies of breast cancer patients with pCIA at least 6 months after completion of chemotherapy, with prospectively designed evaluation of physical exam, history, labs and health-related quality of life	-coherence
Fonia (2017) ⁹³	9		1			2b. (paper) Retrospective case study of pCIA in breast cancer patients lasting more than 6 months after the end of chemotherapy with taxotere/docetaxel regimens and hormonal treatment. The follow-up was more than 18 months post-	-consistency -specificity -temporality -plausibility -coherence

⁹³ Athina Fonia, et al., *Permanent alopecia in patients with breast cancer after taxane chemotherapy and adjuvant hormonal therapy: Clinicopathologic findings in a cohort of 10 patients*. J Am Acad Dermatol, 2017. **76**(5): p. 948-957.

						chemotherapy in all patients.	
Miteva (2011) ⁹⁴	6					2b. (paper) Retrospective Case studies of patients with pCIA post-adjuvant chemotherapy completed at least 12 to 24 months prior to referral to a dermatology clinic for permanent alopecia.	-temporality -plausibility -coherence
Tallon (2010) ⁹⁵	1					2b. (paper) Retrospective Case report of permanent alopecia in patient with breast cancer to identify risk factors and describe histopathology	-specificity -temporality -plausibility -coherence

⁹⁴ Mariya Miteva, MD et al., *Permanent Alopecia After Systemic Chemotherapy: A Clinicopathological Study of 10 Cases*, 33(4) AM. J. DERMATOPATHOL. 345 (2011).

⁹⁵ Ben Tallon, MBChC et al., *Permanent Chemotherapy-Induced Alopecia: Case Report and Review of the Literature*, 63(2) J. AM. ACAD. DERMATOL. 333-36 (2010).

Werbel (2018) ⁹⁶	1					2b. (paper) Retrospective case report	-temporality -plausibility
Masidonski & Mahon (2009) ^{97,98}	11				2	2b. (letter to editor) Retrospective comparative review of non-randomized breast cancer patients treated at their institution over a 10 year span who had permanent alopecia and identify regimen used	-specificity -consistency -temporality -plausibility -coherence
Palameras (2011) ⁹⁹	5					2b. (letter to editor) Retrospective case studies of patients attending a hair clinic with cancer and a diagnosis of pCIA	-temporality -plausibility -coherence

⁹⁶ Tyler Werbet et al., *Persistent Alopecia in a Breast Cancer Patient following Taxane Chemotherapy and Adjuvant Endocrine Therapy: Case Report and Review of Post-treatment Hair Loss in Oncology Patients with Breast Cancer*, *Cureus* 10(7): e3056,(2018).

⁹⁷ Pat Masidonski and Mahon, *Permanent alopecia in women being treated for breast cancer*. *Clin J Oncol Nurs*, 2009. **13**(1): p. 13-4.

⁹⁸ Personal communication with author Mahon on October 2, 2018: all of the taxane-based regimens were Taxotere.

⁹⁹ Ioulios Palamaras, MD et al., *Permanent Chemotherapy-Induced Alopecia: A Review*, 64(3) *J. AM. ACAD. DERMATOL.* 604 (2011).

Tosti (2013) ¹⁰⁰	2					2b. (letter to the editor) Retrospective case reports of pCIA in patients with breast cancer, not previously reported	-temporality -plausibility -coherence
Prevezas (2009) ¹⁰¹	1	1				2b. (letter to editor) Retrospective Case reports	-temporality -plausibility -coherence
TOTAL (100%)	347	51	4	93	54	Strength of association	
TOTAL (81% applied to Freites-Martinez numbers)	341	42	4	93	51		
Other than the F-M paper, with methodologic issues described in the narrative section below, there are no published studies showing an increased number of PCIA as compared to Taxotere/docetaxel. There are no cases of PCIA for either gemcitabine or for bevacizumab. Overall, the number of published cases of PCIA in Taxotere/docetaxel-based regimens are 6.4 to 6.7 times higher than in non-Taxane based regimens and are 6.8 to 8.1 times higher than in the Taxol/paclitaxel-based regimens. In four studies in which comparisons within the study of Taxotere vs. non-Taxotere based regimens could be evaluated (Crown, Kang, Martin, and Sedlacek) the odds ratio of PCIA in the separate studies are 1.37 (Crown), 8.01 (Kang), 3.61 (Martin) and 54.7 (Sedlacek) ¹⁰² .							

¹⁰⁰ Antonella Tosti, MD et al., *Docetaxel and Permanent Alopecia*, 68(5) J. AM. ACAD. DERMATOL. e151 (2013).

¹⁰¹ Christos Prevezas et al., *Irreversible and Severe Alopecia Following Docetaxel or Paclitaxel Cytotoxic Therapy for Breast Cancer*, 160 BRIT. J. DERMATOL. 881 (2009)

¹⁰² Odds Ratio (OR) from the Crown, Martin and Sedlacek studies were calculated by Dr. Madigan. The OR in the Kang paper was provided in the paper. A random effects meta-analysis of these 4 studies, conducted by Dr. Madigan, yielded an OR of 4.13, 95% CI (1.44,11.81), p = 0.008.

D. Brief Narratives of Clinical Studies

Nabholtz (2001): A phase 2 single arm clinical trial investigated the efficacy and toxicity of Taxotere/docetaxel with doxorubicin and cyclophosphamide (TAC) as first-line chemotherapy for anthracycline-naïve patients with metastatic breast cancer. Of the 54 patients treated, the most common treatment-related chronic non-hematologic toxicity was alopecia, with long-lasting (longer than 2 years) partial alopecia occurring in 4 (7.4%) patients.

Bertrand (2013): A prospective clinical study of scalp cooling investigated 79 patients treated with fluorouracil, epirubicin, cyclophosphamide and docetaxel for early stage breast cancer between July 2005 and December 2007 were included in this study. All patients received scalp cooling during chemotherapy, and all patients underwent a clinical examination and photographs of the scalp 5 years after the end of chemotherapy. 26 patients (32.9%) had permanent alopecia, which was severe in 3 patients, moderate in 2 patients, and minimal in 21 patients.

Kang (2018): A prospective cohort study, from February 2012 to July 2013 was conducted at the Samsung Medical Center in Seoul, Korea, of 61 consecutive patients with early stage breast cancer expected to receive adjuvant chemotherapy at the outpatient breast cancer clinic. The objective of the study was to estimate the long-term incidence of permanent chemotherapy-induced alopecia (PCIA) in a cohort of patients with breast cancer whose hair volume and density were measured prior to chemotherapy and who were followed for 3 years after chemotherapy.

The patients received one of the following regimens: 1) doxorubicin and cyclophosphamide (AC); 2) fluorouracil plus cyclophosphamide and doxorubicin (FAC), or 3) doxorubicin and/or cyclophosphamide plus Taxotere/docetaxel). There were 32 patients who received a Taxotere-based regimen, and 29 who received an AC or FAC regimen.

Patients were assessed prior to chemotherapy on the first day of chemotherapy, after 2 cycles of chemotherapy, at 1, 3, and 6 months after completion of chemotherapy and at 3 years after completion of chemotherapy. At each visit, hair density and hair shaft diameter were objectively quantified by a phototrichogram using a Folliscope.¹⁰³ The study defined PCIA as

¹⁰³ Danbee Kang et al., *Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study*, 23 THE ONCOLOGIST 1-7, 2 (2018).

absent or incomplete hair regrowth at ≥ 6 months after chemotherapy. Incomplete hair regrowth was defined as hair density or thickness was two standard deviations (SDs) or more below the baseline mean (before chemotherapy).¹⁰⁴

To isolate the impact of chemotherapy on PCIA, the study excluded patients at baseline who had alopecia, atopic dermatitis, psoriasis, or infectious skin diseases, as well as patients who were taking steroids, antihistamines, antidepressants, or anticonvulsants.¹⁰⁵

The study results demonstrated that patients receiving Taxotere-based treatment had about eight times higher odds of PCIA 3 years after completion of chemotherapy (OR 8.01; 95% CI, 1.20–53.26, $p < .05$) adjusting for age, hair density, and thickness at diagnosis.¹⁰⁶ There were 23 cases of PCIA in the Taxotere/docetaxel group and only 3 with the AC regimens.

Martín (2018): 492 breast cancer patients with adjuvant treatment for breast cancer were studied for the prevalence of permanent chemotherapy-induced alopecia (PCIA) in 1 institution in Spain between December 2005 and May 2006. Two other institutions in Spain joined the prevalence study later to confirm the prevalence of grade 2 permanent alopecia. Grade 2 permanent alopecia was defined as complete alopecia that requires a wig after at least 18 months from the end of chemotherapy. Taking all 3 institutions together, the overall grade 2 PCIA occurred in 36 (10%) of 358 patients with Taxotere/docetaxel regimens reaching cumulative doses of ≥ 400 mg/m² but not in 59 patients receiving lower cumulative doses (300 mg/m²) of Taxotere/docetaxel (e.g., dose response). The study also addressed the issue of whether regimens containing doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) cause permanent alopecia in the absence of Taxotere/docetaxel. In the 306 patients receiving other chemotherapy regimens (including AC/EC regimens alone or followed by paclitaxel) there were no cases of grade 2 permanent alopecia. The study also looked at patients receiving endocrine therapy. There were no patients with grade 2 permanent alopecia who received endocrine therapy without chemotherapy. The incidence of Taxotere/docetaxel-induced grade 2 permanent alopecia was similar in patients with (22/221, 9.96%) and without endocrine therapy (14/137, 10.2%). The median follow-up of patients after the end of chemotherapy was 43 months (range 18-60 months).

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

¹⁰⁶ *Id.* at 3.

Kim (2017): This study was a cross-sectional survey retrospectively identifying early breast cancer patients who had received doxorubicin, cyclophosphamide alone or followed by a taxane as neoadjuvant or adjuvant chemotherapy and were at least 6 months after cessation of chemotherapy, with follow-up from completion of chemotherapy ranging from 6 months to 5 years. A questionnaire regarding alopecia as well as the measurement of hair density was conducted. Among the 265 patients who responded to the questionnaire, 19 (7.2%) reported severe alopecia (>50% of their scalp and lasting at least 6 months after the end of chemotherapy). Of those reporting severe alopecia, 2.7% had received doxorubicin and cyclophosphamide and 10.5% had also received a taxane. In the taxane regimens, 33.3% wore wig vs. 10.7% on non-taxane regimen. Table 1 from the paper notes that 122 of the 265 patients had chemotherapy-induced alopecia, and of this number 29 had not received a taxane-based regimen, and 93 had received a taxane-based regimen. Multivariate analysis showed only the chemotherapy regimen containing a taxane as an independent risk factor for pCIA (OR 4.75, with 95% CI 2.29 - 9.86, $p < .001$). There was no significant difference for endocrine treatment. Neither the publication, nor direct personal communication with the senior author revealed the attribution by specific taxane.¹⁰⁷

Bourgeois (2010): A retrospective study, from May 2008 to May 2010, in which 108 cases of persistent alopecia or suboptimal hair regrowth after adjuvant chemotherapy were reported from 15 different institutions in OMIT (a network in France of the Drugs and Emerging Therapeutics Observatory). Of these 108 cases, 104 (96%) had received Taxotere/docetaxel – based treatment as adjuvant chemotherapy for their breast cancer. Of the 50 patients who answered a questionnaire, 38% to 45% complained of a moderate to severe alteration of the quality of their family and social lives. One year earlier (2009), Bourgeois had reported 61 of 63 cases after adjuvant chemotherapy with a Taxotere-containing regimen (fluorouracil + epirubicin + cyclophosphamide followed by Taxotere). In a presentation for the 37th Annual CTRC-AACR San Antonio Breast Cancer Symposium in 2014, Bourgeois provided an update on ERALOP, a retrospective study using a self-questionnaire targeting patients treated with FEC – Taxotere/docetaxel from 2008 to 2009 to estimate the incidence of persistent significant alopecia at 6 months after the last course of chemotherapy. 829 patients received a questionnaire and 653 (79%) responded. Six months after the last Taxotere/docetaxel course, persistent significant alopecia grade 2 was 8.6% (71 patients) and grade 1 was 32.6% (271 patients). At a median follow-up of 3.7 years, persistent significant alopecia grade 2 was 3.5% (29 patients) and grade 1 was 30% (248 patients).

¹⁰⁷ See footnotes 84 and 85, above.

Sedlacek (2006): A retrospective evaluation of consecutive treatment of 496 women with localized breast cancer. The patients were treated by Sedlacek from January 1994 through December of 2004 in a retrospective prospective controlled cohort study of consecutive patients. The chemotherapy regimens compared: Group A- 258 patients administered doxorubicin and cyclophosphamide regimens without taxanes (AC, FAC, A/CMF). Group B- 126 patients administered doxorubicin and cyclophosphamide plus paclitaxel/Taxol (AC/T, AT/T, AC/T dose dense, ATC, AC/Herceptin). Group C- 112 patients administered doxorubicin and cyclophosphamide plus docetaxel/Taxotere (AC/Tax, ATax, ACTax, AC/TaxXeloda, AC/Tax Herceptin, ATax/FAC, FAC/Tax). Women who underwent high-dose chemotherapy with stem cell rescue were excluded. Only patients with at least 1 year of follow-up post adjuvant chemotherapy were included. The average time from the last dose of chemotherapy was 48 months (range 19 to 85 months). Persistent significant alopecia, defined as <50% hair regrowth at least one year after chemotherapy, developed in 7/112 (6.3%) women with localized breast cancer treated with a Taxotere/docetaxel/doxorubicin/cyclophosphamide containing regimen. All were reported to be wearing wigs. No persistent significant alopecia occurred in those treated with a Taxol/paclitaxel/doxorubicin/cyclophosphamide -containing regimen, or in those treated with a doxorubicin/cyclophosphamide regimen without a taxane.

Crown (2017): Retrospective non-randomized cohort study of 300 patients with early stage breast cancer treated with adjuvant therapy with 3 different treatments. A telephone interview survey (approved by the Hospital audit committee) was conducted of early stage breast cancer patients recorded in their database (St. Vincent University Hospital, Dublin, Ireland) who had completed adjuvant or neo-adjuvant anthracycline and/or taxane-based chemotherapy on clinical trials more than 1 year earlier and assessed as to the number and severity of ongoing alopecia. Drug regimens were assessed with the following categories: Docetaxel regimen in 265 patients, anthracycline-non taxane regimen in 12 patients, and anthracycline + paclitaxel regimen in 23 patients. Alopecia persisting more than 1 year after the completion of chemotherapy was demonstrated in 40 patients in the docetaxel regimen, 1 patient in the anthracycline-non-taxane regimen, and 3 patients in the paclitaxel regimen. For the 191 patients receiving docetaxel and non-anthracycline regimen, there were 2 levels of cumulative exposure of the docetaxel. The alopecia was significantly increased e.g., dose response was demonstrated, with the higher cumulative dose of docetaxel i.e., at 300 mg/m² (97 patients) the incidence was 7%, all grade 1, and at a dose of 450 mg/m² (94 patients) it was 20% with a higher grade of alopecia (6% grade 2, 14% grade 1).

Thorp (2015): This retrospective study of prospectively evaluated patients (presented at the CTRC-AACR San Antonio Breast Cancer Symposium in 2014), used a questionnaire sent in October 2013 to 189 patients who had received docetaxel-based regimens for early stage breast

cancer in 2010 at their regional cancer center. The aim of the study was to determine the incidence, site, extent and duration of hair loss. Of the 189 questionnaires sent, 134 (71%) were returned. Of the respondents, 21 (15.8%) noted significant scalp hair loss, 13 (9.8%) gave equivocal responses, 99 (77.4%) had no significant scalp hair loss, and 1 patient did not answer the scalp hair loss question. 16 patients noted use of wigs and hair extensions. Lack of hair was also noted for a subset in other body areas, such as eyelashes and eyebrows. Long-term hair loss (up to 3.5 years after the last chemotherapy with a Taxotere/docetaxel regimen) occurs in 10 to 15% of patients, and from responses to the questionnaire questions, had a significant impact on the patients' quality of life. Univariate and multivariate analyses showed no significant association with other patient or treatment characteristics (e.g., endocrine treatment).

Freites-Martinez (2019): Eight-year retrospective, multicenter case study conducted between January 2009 and July 2017 in patients referred to the dermatology service from two comprehensive cancer centers and one tertiary-care hospital. The institutions included Memorial Sloan Kettering, New York, the Institut Universitaire du Cancer, Toulouse, France and the dermatology service at University Federico II, Naples, Italy. Patients were eligible if they received only systemic cytotoxic chemotherapy with a clinical diagnosis of PCIA or received chemotherapy followed by endocrine therapies, but the alopecia was associated with endocrine therapy. Standardized photographs of the scalp, trichoscopy to assess hair diameter and hair density, and quality of life evaluations were conducted. Of 385 patients, 193 were excluded, and 192 included, including 98 with persistent alopecia attributed solely to chemotherapy, and 94 with alopecia attributed solely to endocrine therapy. Exclusions included 82 for chemotherapy-induced alopecia, 40 for other potential causes of alopecia (e.g., androgenetic, thyroid-related, telogen effluvium, targeted therapy, immunotherapy, and graft-vs-host disease) 35 for missing data, 19 with previous scalp radiotherapy, and 17 for having a combined attribution of alopecia from cytotoxic chemotherapy and endocrine therapy. 79 (81%) of the 98 patients with PCIA had a diagnosis of breast cancer, and 89 (95%) of the 94 with alopecia attributed to endocrine therapy had a diagnosis of breast cancer. The most common agent associated with PCIA was taxane-based chemotherapy (80 patients with 47 on paclitaxel, 31 on docetaxel, and 2 with both), and grade 2 alopecia was seen in 29 of 75 patients. It was not clear from the methods section how the 385 patients were identified, nor the methodology for excluding more than half of the patients. In addition, the loss to follow-up on the subset of 98 patients with PCIA was not explained. Of the 98 in the PCIA category, only 75 of the 98 had clinical characteristics of their alopecia noted, only 45 of the 98 had trichoscopy performed, and only 41 of the 98 had data on quality of life; it was not clear how many in the subset of 75 or 45 or 41 patients had a diagnosis of breast cancer, and the specific regimen used.

Kluger (2012): This retrospective study analyzed the clinical and histological features of severe permanent alopecia that was diagnosed between 2007 and 2011 in 20 breast cancer patients receiving treatment of fluorouracil + epirubicin + cyclophosphamide followed by Taxotere/docetaxel. One of the 20 had also received Taxol/paclitaxel, in addition to Taxotere/docetaxel. Permanent alopecia was defined as absent or incomplete hair regrowth at \geq 6 months post-chemotherapy. Health-related quality of life (QoL) was assessed by a self-administered questionnaire, the Dermatology Life Quality Index (DLQI) and by whether or not the patient permanently wore a medical hair prosthesis (wig). The DLQI is a validated, rapid and highly sensitive test used in routine clinical practice to evaluate the QoL for various skin diseases, and evaluates 10 items, with higher scores indicating greater impairment of QoL. The mean DLQI in 18 patients administered the test was 8.66, compared to a mean of 0.5 in a healthy population. Severe impairment was reported by 7 of the 18 patients (38%, score 11-20). 70% (14/20) wore a hair prosthesis (i.e., a wig) or scarf (1 patient).

Fonia (2017): This retrospective study incorporated data from April 2010 through August 2013 and identified 10 breast cancer patients treated with Taxotere/docetaxel-based regimens (1 also received paclitaxel in addition to Taxotere/docetaxel) who developed permanent alopecia lasting more than 6 months after the end of chemotherapy. The follow-up was more than 18 months post-chemotherapy in all patients. Of the 10 patients with PCIA, all received docetaxel regimens - 5 had no endocrine therapy, 7 had no anthracycline, and 4 had neither an anthracycline or cyclophosphamide. One had received 3 cycles of docetaxel and 1 cycle of paclitaxel. All 10 patients had alopecia of the scalp, and 3/10 also had hair loss of eyebrows and eyelashes and 5/10 had loss of body hair. All patients had diffuse hair loss on their scalp with residual sparse hair. After the end of chemotherapy, hair regrowth was partial in 9 of 10 patients, with minimal regrowth in 1 patient. The patient wore a wig and had slow but complete hair regrowth within 6 months after starting treatment with topical minoxidil.

Miteva (2011): Describes a retrospective clinicopathological study of 10 cases of permanent alopecia after systemic chemotherapy, in which 6 cases were breast cancer patients treated with Taxotere/docetaxel. The histologic findings of permanent alopecia after chemotherapy were those of a nonscarring alopecia. The cases came from patients who were referred for treatment of hair loss to the Department of Dermatology (9 cases in Bologna, Italy and 1 case in Miami, Florida). All were evaluated at least 12 to 24 months after the end of chemotherapy. The severity of hair loss ranged from very severe to severe, and all women patients wore a wig.

Tallon (2010): This case report was of a woman with breast cancer, negative for ER and PR and on no endocrine therapy and no anthracycline, presenting with persisting alopecia 13 months after completion of adjuvant chemotherapy with a Taxotere/docetaxel-containing regimen. She had no prior history of hair loss and had no pre-existing hair loss. Two weeks after the start of

her chemotherapy, she began to lose the hair on her scalp, as well as her eyebrows, eyelashes and body hair. By the completion of her chemotherapy, she was completely bald. She experienced some regrowth of her hair but required the use of a scalp prosthesis (wig). Physical examination revealed severe diffuse hair loss, most prominent over the crown.

Werbel (2018): A case study of a 59 yo woman with ER+, PR+ and Her-2+ invasive breast cancer that was treated with surgery, radiation, docetaxel-containing regimen (pertuzumab, docetaxel, carboplatin followed by trastuzumab and currently on neratinib) and adjuvant hormonal therapy (starting with anastrozole and switching to tamoxifen). She noted hair loss beginning after the first course of systemic chemotherapy, that became more extensive throughout the remainder of her treatment and had not experienced any regrowth of scalp hair at the time she was diagnosed with persistent alopecia 15 months later. Scalp biopsies were consistent with a non-scarring alopecia.

Masidonski and Mahon (2009): Retrospective evaluation of cases over the past 10 years, 13 women treated for breast cancer at their institution have been identified with permanent alopecia, and 11/13 had been treated with a Taxotere/docetaxel-based regimen with an anthracycline and cyclophosphamide, and the other 2 with an anthracycline and cyclophosphamide. 7 were not on any endocrine therapy, and 6 were ER/PR positive and were on aromatase inhibitors.

Palamaras (2011): This was a retrospective review of 8,430 records of patients who had attended a Hair Clinic during the previous 7 years with non-scarring alopecia, to identify cases of chemotherapy-induced permanent alopecia (PCIA). Seven cases of PCIA were identified (in patients treated for breast cancer, and for germ cell tumors); 2 occurred following treatment with busulphan and 5 were following treatment with Taxotere/docetaxel-regimens, combined with either Cisplatin, an anthracycline, or an anthracycline plus cyclophosphamide). All 7 cases showed short and sparse scalp hair, which developed a few weeks after the start of chemotherapy. Scalp biopsy revealed a marked reduction in follicular units.

Tosti (2013): Reported two new cases of permanent alopecia following a docetaxel-based chemotherapy regimen for patients with breast cancer (an additional 5 cases had already been reported in the Palamaras study, in which Tosti was a co-author, in 2011).

Prevezas (2009): This report noted 2 cases reports of severe and irreversible alopecia following chemotherapy with the taxanes, docetaxel or paclitaxel, for the treatment of recurrent breast cancer. The patient treated with docetaxel was 7 years out from her treatment. The patient treated with paclitaxel was 3 years out from her treatment.

Below are narratives of published studies provided by Sanofi defense counsel that I reviewed and found lacking in critical details important for interpretation e.g., lacking in identifying the chemotherapy given to breast cancer patients, and/or lacking in identifying the numbers of breast cancer patients receiving a particular chemotherapy regimen, and/or lacking in evaluating the endpoint of interest, persistent, irreversible, or permanent alopecia.

Berglund (1991)¹⁰⁸ Retrospective study, in which a questionnaire was mailed to 448 premenopausal and postmenopausal patients, free from recurrence 2 to 10 years after having received adjuvant therapy with 1976 era regimens of chemotherapy and radiation therapy, to which they had been randomized. The questionnaire study was done 2-10 years after treatment. The aim was to investigate differences in aspects of quality of life, and their hypothesis was that chemotherapy would be associated with late consequences in the form of more physical, mental and social problems compared to radiotherapy.

Patients aged below 71 years with positive lymph nodes and/or a tumor exceeding 3 cm were randomized to postoperative radiotherapy to the chest wall and regional nodes (46 Gy/4-5 weeks) or to 12 courses of chemotherapy (CMF: cyclophosphamide, methotrexate and 5-fluorouracil). In addition, the postmenopausal patients were included in a concurrent randomized comparison of adjuvant tamoxifen (40 mg daily for 2 years) versus no adjuvant endocrine therapy. From 1976 to 1985, a total of 849 patients were included in the trial. There were several changes to the study over the ensuing years, including: from 1978 onward, the upper age limit was lowered to 65 years, because it was found that older patients could not complete the protocol chemotherapy due to toxicity; in 1978, the chemotherapy course interval was changed from 6 to 4 weeks, which shortened the total treatment time from 1.5 years to 1 year; in 1985, the chemotherapy regimen was changed from 12 to 6 courses. The reason was that data from other studies indicated that adjuvant CMF for 6 months was as efficient as CMF for 12 months; and due to restricted radiotherapy resources, a 2:1 randomization rather than a 1:1 randomization of chemotherapy: radiotherapy was performed from March 1982 to May 1985. The total number of randomized patients was thus higher in the chemotherapy group than in the radiotherapy group (475 vs. 374 patients).

The quality of life study was on the subset of relapse-free survivors: 245 chemotherapy and 203 radiotherapy patients. Out of the 448 mailed questionnaires, the final number of returned

¹⁰⁸ Gunilla Berglund et al., *Late Effects of Adjuvant Chemotherapy and Postoperative Radiotherapy on Quality of Life among Breast Cancer Patients*, Eur J Cancer, Vol. 27, No. 9, pp.1075, 1991

completed questionnaires was 382 (83%), which included 201(82%) in the chemotherapy group and 172 (85%) in the radiotherapy group. A Swedish questionnaire with criteria addressing physical symptoms (of disease and treatment), psychic well-being, physical and social activities and quality of life, and a confirmed high reliability and validity, was not available. A questionnaire that had not been previously used was constructed for this study. There were no questions on irreversible, persistent, or permanent alopecia. Among the 32 items on the symptom list, alopecia is included, and the language is as follows: *Symptom list (32 items)*. Score your intensity of: fatigue, decreased stamina, pain, changes in physical appearance, joint problems, problems with the scar, infections, hair loss, sleeping problems, memory problems, concentration problems, nausea, smell aversion, food aversion, worries about health, and anxiousness. Added in 1988 were: weight increase, weight loss, decreased appetite, gastritis, diarrhea, dysphagia, urinary tract problems, cystitis (urinary), decrease in sexual desire, decrease in sexual ability, irritation of mouth and throat, skin irritation, dry skin, headache, dizziness and irritability. Of note, there was no difference in degree of symptoms or problems related to the question of alopecia between patients on the radiotherapy arm or those on the chemotherapy arm – it was 17%. So even though persistent, irreversible or permanent alopecia issues were not addressed, even asking a question about hair loss at 2 to 10 years out from their primary treatment did not differ according to whether or not they received chemotherapy or radiotherapy.

Overall, the investigators noted in their paper that they found no support for their hypothesis that chemotherapy with CMF would lead to more severe late consequences than radiotherapy. My conclusion after reviewing this paper, is that no relevant questions were asked regarding permanent, irreversible or persistent alopecia, and that even given all the faults in the study design, there was no difference noted on alopecia that was detected between the total number of patients who had received radiotherapy to the breast vs. those who had received chemotherapy with CMF.

Yagata (2015)¹⁰⁹: A retrospective study using a questionnaire was distributed to patients in hospitals throughout Japan between April and October 2013, posing questions regarding the current status of the patients' appearance. Eligible patients were women with breast cancer without any recurrence who had received adjuvant or neoadjuvant chemotherapy containing an anthracycline and/or taxanes (either paclitaxel or docetaxel), and who were within 5 years from their last chemotherapy treatment. The physicians at each hospital asked their patients to fill

¹⁰⁹ Hiroshi Yagata et al., Abstract P5-15-17: *National survey of long-term recovery from chemotherapy-induced hair loss in patients with breast cancer*, Cancer Res. AACR journals.org/content/Vol 75/Issue 9_Supplement/P5-15-17, 2015

out the questionnaire and mail it directly to the data center. The status of scalp hair was analyzed in a cross-sectional manner according to the duration from chemotherapy. 1853 questionnaires were sent, and 1511 patients returned the questionnaires, and in total 1478 questionnaires were analyzed. The actual questionnaire survey was not provided, but in the abstract they provided responses to some of the questions, which included the following: 13.1% noted hair growth beginning during chemotherapy, and 80.3% after chemotherapy ended, although 6.6% left the question unanswered. Within 6 months of the start of hair growth, 65% felt a change in hair thickness, 70% felt a change in quality, 40% noted it had become “unruly”, 44% a color change, and 80% noted growing more gray hair.

There was no attribution of the numbers of the 1478 patients who had received taxane or non-taxane regimens, and by the questions posed, it appeared that none of the questions asked about the type or severity of hair loss.

Beseicker (1997)¹¹⁰: Retrospective study examined side effects of chemotherapy as perceived by 21 early stage breast cancer patients in order to determine which side effects persisted after chemotherapy and whether any new side effects were experienced after therapy ended. They explored the following research questions: (1) What side effects were most significant to patients during chemotherapy? (2) Were these side effects expected? (3) How did patients respond to the side effects they experienced? (4) What feelings were experienced at the end of chemotherapy? (5) What side-effects, if any, persisted or developed after chemotherapy? Patients had received CMF (57%), CAF (24%) and FuVMiC (19%) and interviewed twice, once 1 month after chemotherapy had ended, and the other at 6 months after chemotherapy had ended. 18% (3 patients) noted hair “problems” characterized as different color, different texture or uneven, and none viewed these issues as the most significant side effects.

There was no mention in the article of the type or severity of hair loss, nor clear questions relating to the pertinent issue of permanent hair loss.

Jung (2013)¹¹¹ Retrospective study of 54 patients, men (25 patients) and women (29 patients), ages ranging from 1 year to over 61 years old, diagnosed from January 1996 to December 2011 with PCIA, all having visited a dermatology clinic in Korea from 6 months to 168 months after the discontinuation of chemotherapy, due to the continuation of alopecia. The average age for

¹¹⁰ Analee Beisecker, *Side Effects Of Adjuvant Chemotherapy: Perceptions Of Node-Negative Breast Cancer Patients*, *Psycho-Oncology*, Vol. 6: 85–93 (1997).

¹¹¹ Mi Young Jung, MD., et al. *A Clinical Study of Chemotherapy- Induced Permanent Alopecia*, *Korean Journal of Dermatology* 2013;51 (12):933 -938.

men was 26.2 years and for women 36.1 years, with 20 patients under the age of 20 years, 17 between the ages of 21 and 40 years, 15 between the ages of 41 and 60 years, and 2 older than age 61. There were 9 different types of cancer, as well as autoimmune disease. 12 of the 54 patients had breast cancer. The age, gender, duration of alopecia, familial history of alopecia, past medical history (including the types of chemotherapy agents), clinical patterns of alopecia and treatment responses were all analyzed. 38 of the patients were treated with combination chemotherapy, 16 were treated with monotherapy alone. Eight (15%) had been treated with stem cell transplantation, and 10 (18.5%) had been treated with radiation therapy to the scalp.

There was no attribution of the type of chemotherapy given for the indication, no indication of the extent of disease (whether localized or metastasized) and since the chemotherapy given with stem cell transplantation, and radiation to the scalp is already known to cause pCIA, this study was lacking in critical information.

During the time these studies were being published, the European Medicines Agency (EMA) had ongoing iterative discussions with the company regarding PCIA.

I had access to Sanofi's review of their global pharmacovigilance database that they conducted in 2011 and in 2015.¹¹² Sanofi used different terms and time duration to assess for PCIA in 2011 and in 2015, and interestingly, there is no overlap of case report identifiers in 2011 and in 2015.

In January 2011, Sanofi provided an analysis of irreversible alopecia through December 2010. Of 1,620 cases retrieved using the high level term alopecias, the search identified 142 reports of irreversible alopecia defined as not recovered 12 or more months after the last dose of Taxotere/docetaxel chemotherapy. The analysis excluded 1060 cases where the outcome was unknown and 418 reports where the latest outcome was reported less than 12 months after the last dose of chemotherapy. In that analysis Sanofi concluded that Taxotere/docetaxel alone was not the sole cause of the irreversible alopecia.

In November 2015, Sanofi provided an analysis through October 2015. Of 2,173 cases retrieved using the high level term alopecias, the search identified 117 reports in which the verbatim term included either "permanent" or "irreversible" or alopecia that lasted more than 2 years. The analysis excluded 1,320 cases where the outcome was unknown. The 117 cases of permanent or irreversible alopecia represented 5.3% of the total cases of alopecia. The data includes cases of

¹¹² Emanuel Palatinsky, MD, Global Safety Officer, "Clinical Overview: Docetaxel – Persistent Alopecia", Sanofi_04353204; and Nanae Hangai, MD, PhD, Global Safety Officer, "Clinical Overview: Docetaxel and Permanent Alopecia." Sanofi_00829563, respectively.

Taxotere monotherapy-induced persistent alopecia. 70% of the patients with PCIA were on combination chemotherapy regimens with Taxotere, but 30% were not on any other chemotherapy other than Taxotere. Based on their review of the Sanofi global pharmacovigilance database, worldwide scientific literature, clinical studies, and biologic plausibility, Sanofi noted that

“[T]he cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.”¹¹³

IX. Assessment of Causation using Bradford Hill Criteria

I used the nine criteria described in Section IVE¹¹⁴ to assess the causal relationship between Taxotere/docetaxel and permanent chemotherapy-induced alopecia in patients receiving chemotherapy for their early stage breast cancer. The totality of evidence included the company’s own randomized clinical trials in early stage breast cancer, 19 published papers from a comprehensive worldwide medical search and review of the topic, and safety reports provided to Sanofi through their global pharmacovigilance database:

- 1) strength of association from the randomized clinical trials TAX 316 and GEICAM 9805, together show an almost doubling of the odds of PCIA with the Taxotere/docetaxel regimen compared to the control arm; a quadrupling of the odds in studies in which a comparator arm within the study could be evaluated (OR 4.13 from Crown, Kang, Martin and Sedlacek, with individual OR of 1.37, 8.01, 3.61 and 54.7 respectively), with a 6.4 to 8 times increased number of reported cases in the 19 published studies.
- 2) consistency of results across the randomized clinical trials, published studies, and pharmacovigilance analyses
- 3) specificity of the outcome of permanent chemotherapy-induced alopecia to the Taxotere/docetaxel. The randomized clinical trials and the published studies, particularly those in which a comparator arm without Taxotere/docetaxel, show an increased risk that the PCIA is due to the Taxotere/docetaxel and not to the other chemotherapies used in the Taxotere/docetaxel regimens

¹¹³ Nanae Hangai, MD, PhD, Global Safety Officer, “Clinical Overview: Docetaxel and Permanent Alopecia.” Sanofi_00829563.

¹¹⁴ See section IV.E

- 4) temporality of the Taxotere/docetaxel exposure preceding the event of permanent chemotherapy-induced alopecia; All of the studies demonstrate that the Taxotere/docetaxel exposure preceded the outcome event of PCIA
- 5) gradient, or dose-response, that increased cumulative exposure of Taxotere/docetaxel, i.e., that 400 mg/m² or 450 mg/m² leads to a greater incidence and more severe degree of permanent chemotherapy-induced alopecia than 300 mg/m² or less; Papers supporting this criteria come from the Crown and Martin papers.
- 6) biologic plausibility for Taxotere/docetaxel causing permanent chemotherapy-induced alopecia, i.e., is already well known and documented to cause alopecia, and substantial biologic plausibility for a proposed mechanism of action for destruction of the hair follicle, and hair stem cells or disruption of any of the multiple communication signals between the stem cells; and,
- 7) coherence e.g., does not seriously conflict with the generally known facts of the natural history and biology of the disease.
- 8) experimental – The two randomized clinical trials and retrospective review of prospectively conducted studies in which the treatment is the intervention are examples of using experiments to evaluate the contribution of the treatment intervention to the outcome event of PCIA. I did not identify an experiment of challenge, de-challenge and rechallenge; however, this type of experiment cannot be used in the scenario of toxic chemotherapy
- 9) In terms of the criteria of analogy – I was not able to identify another model in which the totality of evidence, as was seen with Taxotere/docetaxel, was demonstrated to show that conventional chemotherapy causes permanent chemotherapy-induced alopecia.

Therefore, applying these criteria to the approximately 2400 patients in the randomized clinical trials, the several hundreds of patients in the published literature, and over several thousand patients in the safety database, it is my opinion that there is reasonable evidence that Taxotere/docetaxel causes permanent chemotherapy induced alopecia in early stage breast cancer patients. There are no randomized clinical trials of non-taxotere containing regimens showing an increased risk of permanent chemotherapy-induced alopecia in early stage breast cancer patients, and the preponderance of evidence in the published literature of peer-reviewed prospective and retrospective clinical studies show a substantial increased risk of Taxotere/docetaxel, with corroborative evidence in the safety database, with all 3 lines of evidence – from randomized clinical trials, published peer-reviewed literature, and the safety

database, all pointing consistently in the same direction of Taxotere/docetaxel causing an increased risk of permanent chemotherapy-induced alopecia, at a level substantially higher than any of the other chemotherapies utilized in the multi-drug regimen.

Based on my independent review of the worldwide scientific literature, randomized clinical trials in which PCIA was an evaluable endpoint, and Sanofi's pharmacovigilance database, the totality of evidence substantiates the causal association of Taxotere/docetaxel and permanent/irreversible alopecia in patients who received Taxotere/docetaxel-based regimens. The evidence is strong that Taxotere/docetaxel has a much higher odds of causing PCIA than any of the other chemotherapies used in the combination regimens for treatment of breast cancer.

X. Conclusions

Based upon my education, training and experience, it is my opinion to a reasonable degree of certainty that:

1. Early stage operable breast cancer patients, particularly women with ER/PR positive, HER2 negative disease, have an excellent long-term prognosis; for the vast majority of patients, this is not a fatal condition.
2. If chemotherapy is indicated, there are multiple options available as evidenced by NCCN Guidelines, ASCO Guidelines, and published reviews and papers.
3. Taxotere has been shown by reliable scientific evidence to cause permanent chemotherapy-induced alopecia as part of its adverse event profile. PCIA as an adverse event of Taxotere-containing regimens in the adjuvant treatment of women with early stage operable breast cancer (Stages I, IIA, IIB, IIIA) had been known by Sanofi through analysis of its own sponsored randomized clinical trials, pharmacovigilance database, and evaluation of the world-wide literature. Taxotere is causally associated with PCIA by multiple criteria scientifically used to assess causation, as evidenced in the company-sponsored randomized controlled clinical trials, in the multiple published studies from 2001 to the present, and in postmarketing surveillance starting at least in the early 2000s.

4. Reliable scientific evidence from randomized clinical trials, published peer-reviewed literature, and the Sanofi safety database consistently demonstrates a significant increased risk of PCIA with Taxotere/docetaxel. The level of risk of PCIA with Taxotere/docetaxel is substantially higher than any other comparator chemotherapy drugs, including those often used in Taxotere regimens.
5. The company's own analysis of the data, which included their own sponsored randomized clinical trials, published papers, and pharmacovigilance safety reporting, led them to the conclusion that permanent chemotherapy-induced alopecia is causally associated with Taxotere regimens.
6. Physicians and patients need to be well-informed on the risks and benefits of the chemotherapy options, particularly those that can lead to permanent and disfiguring side effects, including permanent chemotherapy-induced alopecia, so that an informed treatment decision can be made.
7. Had they been informed by Sanofi of the risk of permanent chemotherapy-induced alopecia, reasonable physicians would have included a discussion of the risk of PCIA in their benefit-risk interaction with patients about treatment options for their early stage breast cancer, to allow for more informed decisions. This information may have changed the treatment options discussed, and the patient's choice.

I reserve the right to supplement this report.



Ellen G. Feigal, M.D.

October 21, 2019

EXHIBIT H

Filed Under Seal

EXHIBIT H

EXPERT REPORT OF
Laura M. Plunkett, Ph.D., DABT
October 21, 2019

I. Training and Qualifications

1. I am a pharmacologist, toxicologist, United States Food and Drug Administration (FDA) regulatory specialist and principal of a consulting company known as Integrative Biostrategies, LLC. Integrative Biostrategies, based in Houston, Texas, is a consulting firm that works at the interface of biological science, regulatory affairs and business decisions to provide its clients with science-based solutions to issues associated with product development and stewardship. Before joining Integrative Biostrategies in 2001, I was head of the consulting firm known as Plunkett & Associates.

2. I am board-certified as a Diplomate of the American Board of Toxicology. I am a member of several professional organizations and have authored or co-authored numerous scientific publications. I have over twenty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels.

3. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. My doctoral research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides.

4. From June 1984 through August 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory of the National Institute of Mental Health. My research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

5. From September 1986 to June 1989, I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas, where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences. During this time, I studied drugs of all classes. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug actions, both the therapeutic effect and the toxic effects of drugs.

6. From December 1989 to August 1997, I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. I worked specifically within the health sciences group and most of my projects dealt with issues surrounding products or processes regulated by the U.S. Food and Drug Administration (FDA). During my consulting career (ENVIRON, Plunkett & Associates, and Integrative Biostrategies), I have worked on a variety of projects dealing with the regulation of products by the FDA, including human drugs, veterinary drugs, biologics, medical devices, consumer products, dietary supplements and foods. I have advised my clients on regulatory issues and strategies for their products (relating to both Canadian and American regulations), designed preclinical and clinical studies for both efficacy and safety, advised clients on issues related to statements regarding efficacy and warnings for their products based on the current labeling regulations and generally acted as a regulatory affairs staff for small companies in their early stages of product development. A tool common to all my work as a consultant would be risk assessment, including many projects where risks and benefits of human therapeutics were at issue.

7. With respect to my experience that is directly relevant to the issues in this case, I have done a great deal of work on projects that have required me to examine the risks associated with exposure to drugs of all types, including drugs to treat cancer. I have worked on many projects involving mechanisms of carcinogenesis and ways that drugs and chemicals can affect those mechanisms; some of this work has involved obtaining patent protection of new anti-cancer drug products or treatments. I have expertise in pharmacokinetics, including the differences in pharmacokinetics of drugs when they are administered by routes other than oral

ingestion, *i.e.*, intravenous, dermal, inhalation, *etc.* I have lectured to graduate students, law students and pharmacy students on these topics as well.

8. Throughout my career I have published dozens of articles which are listed in my curriculum vitae (attached as Appendix A). In litigation, I have provided expert testimony and been qualified in both state and federal courts in the areas of pharmacology, pharmacokinetics, toxicology, risk assessment and FDA regulations. Also attached to this report as Appendix B is a list of all documents I have reviewed in this case.

II. Information Reviewed

9. During the course of my work on this case, I have reviewed the following materials:

- a) scientific literature relating to the pharmacology and toxicology of taxane drug products, including Taxotere® (docetaxel) and Taxol® (paclitaxel);
- b) documents that are available on the FDA website including documents related to Taxotere's approval, documents related to Taxol's approval, and labeling for a variety of chemotherapeutic drugs that are currently used to treat cancer; and
- c) depositions containing testimony of individuals involved in the litigation, exhibits to those depositions, and a variety of confidential documents produced during the litigation.

It should be noted that all of the sources listed above are ones commonly used in my work as a pharmacologist, toxicologist, and risk assessor. At the end of this report is attached a list of the published articles cited throughout this report. All opinions expressed in this report are expressed based on my training and experience and to a reasonable degree of scientific certainty.

III. Methodology

10. With respect to the methodology I employed while working on this case and in forming my opinions as outlined in this report, I have used standard methods that I apply in all of my work as a pharmacologist and toxicologist, both litigation and non-litigation projects. One tool I use is a method known as human health risk assessment. Pharmacologists and toxicologists

routinely assess both benefits and risks related to exposure to drugs using the risk assessment process. In fact, general principles of pharmacology and toxicology is the scientific core of risk assessment. Risk assessment has been used for decades by a wide variety of governmental bodies. In 1983, the National Research Council (NRC) detailed the steps for risk assessment and described the methodology that is in use today as four basic steps: hazard identification, dose-response assessment, exposure analysis, and characterization of risks (NRC, 1983). As a result, risk assessment is a standard tool used by pharmacologists and toxicologists when they are trying to understand the benefits and risks associated with a drug.

11. Another tool I employed in this project is known as a “weight-of-the-evidence” assessment. A weight-of-the-evidence assessment involves evaluating individual studies and determining what the studies describe, when considered as a whole. Therefore, weight-of-the-evidence methods were critical to defining the literature that identified the benefits and hazards of taxane drug products. In the current case, I examined the Taxotere and Taxol product labeling, regulatory submissions that describe the pharmacology and toxicology of Taxotere, and the scientific literature related to the benefits and risks of taxane drug products and considered the evidence as a whole in my assessment of Taxotere’s risks and benefits. The *Reference Manual on Scientific Evidence* also describes the use of weight-of-the-evidence by experts in the process of evaluating a body of data or studies¹.

12. Based on my review of published scientific literature and other documents in this case, as well as my training and experience as a pharmacologist and toxicologist, I have formed the opinions set out in my report. I reserve the right to supplement my opinions as new information becomes available.

IV. Background on Taxotere and Taxol

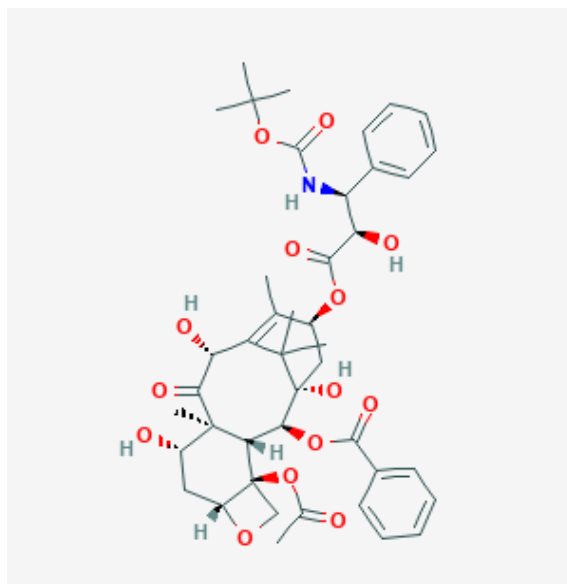
13. Taxotere (NDA² 020449), also known as docetaxel, is a human prescription drug product used to treat various types of cancer. Docetaxel is a semi-synthetic antineoplastic agent that is prepared from a precursor extracted from the renewable needle biomass of yew plants (see

¹ The *Reference Manual on Scientific Evidence*, 3rd Edition. National Research Council. 2011. Washington, DC: The National Academies Press. <https://doi.org/10.17226/13163>.

² NDA = New Drug Application

Taxotere labeling). The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5 β -20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. The structure of docetaxel is shown below in Figure 1:

Figure 1: Structure of Docetaxel



14. Taxotere was approved for use in the United States on May 14, 1996; the sponsor was Rhone-Poulenc Rorer. By 2002, Aventis Pharmaceuticals, Inc., became responsible for the Taxotere NDA; Aventis Pharmaceuticals, Inc. was the company that is now known as Sanofi. Taxotere's patent term now has expired (2015), and generic versions of the drug have become available in the marketplace.

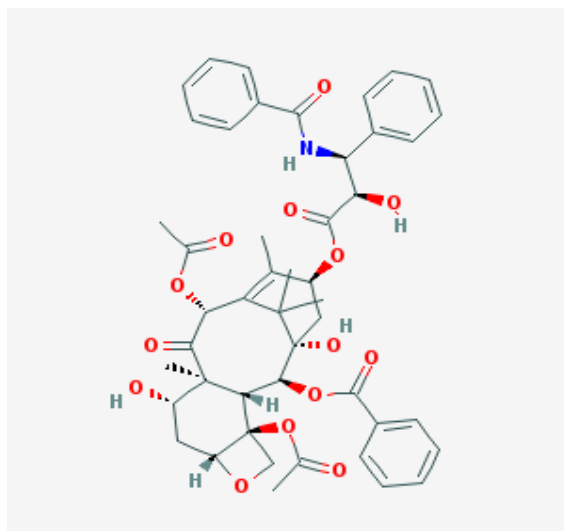
15. Taxotere was initially approved in the United States for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.³ Subsequent FDA approvals for other forms of cancer have included: a) treatment of patients with locally advanced

³ Sanofi applied for FDA approval in July of 1994. FDA initially withheld approval of the drug, citing the need for additional clinical trial data (see Sanofi_00502776; Sanofi_03274084; Sanofi_01382010; Exhibits 1, 2 and 4 to the deposition of Vanina Groult dated March 22, 2018). Sanofi provided additional data, and as a condition to approval, agreed to complete additional controlled clinical trials. See FDA Approval Letter NDA 20-449, May 14, 1996 (Exhibit 3 to the deposition of Vanina Groult dated March 22, 2018). It should be noted that issues that FDA was concerned about were related to patient safety (Taxotere toxicity).

or metastatic small cell lung cancer after failure of prior platinum-based chemotherapy (December 23, 1999); b) treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for the condition (November 27, 2002); c) use in combination with prednisone for the treatment of metastatic, androgen-dependent (hormone-refractory) prostate cancer (May 19, 2004); d) use in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of women with operable node-positive breast cancer (August 18, 2004); e) use in combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction who have not received prior chemotherapy for advanced disease (March 22, 2006); f) use in combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable, locally advanced squamous cell carcinoma of the head and neck (October 17, 2006); and g) use in combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (September 28, 2007). As a result, Taxotere is used to treat many different forms of cancer, often in combination with other drugs.

16. Taxol (NDA 020262), also known as paclitaxel, is another taxane human prescription drug product. It was first approved for use in the United States on December 29, 1992. Unlike Taxotere, Taxol had only an initial five-year exclusivity period (no patent protection was available). Bristol Meyers Squibb (BMS) licensed the product and marketed it here in the United States. Paclitaxel was the original a natural product that was isolated from the bark of the Pacific yew, or the Western yew, tree. Today, it is manufactured as a semi-synthetic drug product. The structure of paclitaxel is shown below in Figure 2:

Figure 2: Structure of Paclitaxel



The chemical name of paclitaxel is 5,20-Epoxy-1,2,4,7,10,13-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. Taxotere, which came after Taxol in terms of discovery, is a derivative of Taxol that is very similar in terms of structure (see Figures 1 and 2 above). The structure of Taxotere differs from Taxol at two positions: 1) the hydroxyl functional group on carbon 10 in Taxotere is an acetate ester in Taxol; and 2) a tert-butyl carbamate ester is found on the phenylpropionate side chain of Taxotere, which is the benzamide in Taxol.

17. Taxol has been approved for the treatment of various types of cancer. Like Taxotere, Taxol is available as a generic drug product. Taxol's first approval was for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy. Subsequent FDA approvals for other forms of cancer have included treatment of non-small cell lung cancer, breast cancer and AIDS-related Kaposi's sarcoma. With respect to breast cancer, Taxol was approved for adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy, and for treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Thus, like Taxotere, Taxol is used in combination with other anti-neoplastic drugs in some cases.

18. In the current case, the indication at issue for Taxotere use is for adjuvant treatment of early stage breast cancer. Therefore, the discussion of these drugs below will focus on that patient population, women with early stage breast cancer, when clinical data are being discussed and the two drugs are being compared with each other.

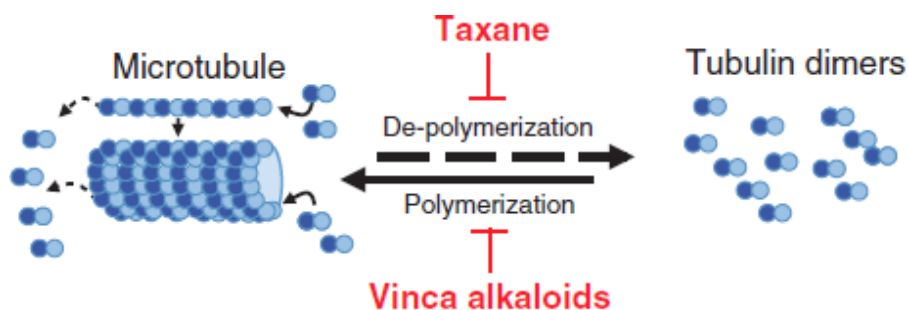
V. Pharmacology and Toxicology of Taxotere and Taxol

19. The taxanes, also referred to as taxoids, are anti-neoplastic drug products whose pharmacology has been described in textbooks (*e.g.*, Chabner *et al.* 2001. Chemotherapy of neoplastic diseases. In: *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th edition*. Hardiman and Limbird (eds.). New York, NY: McGraw-Hill, chapter 52; Chabner *et al.*

2006. Antineoplastic agents. In: *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 11th edition*. Brunton *et al.* (eds.). New York, NY: McGraw-Hill, chapter 51; Wellstein *et al.* 2018. Cytotoxic drugs. In: *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13th edition*. Brunton *et al.* (eds.). New York, NY: McGraw-Hill, chapter 66). Docetaxel and paclitaxel are the agents described in such textbooks under the group of drugs referred to as “natural products”. Natural products in this class are drug products that are either sourced from nature directly or are semi-synthetic or synthetic derivatives of compounds found in nature. The other natural product antineoplastic agents include the vinca alkaloids (*e.g.*, vinblastine, vincristine), camptothecin analogs (*e.g.*, topotecan, irinotecan), epipodophyllotoxins (*e.g.*, etoposide, teniposide), and some antibiotics (*e.g.*, daunorubicin, doxorubicin, bleomycin, mitomycin C).

20. Taxanes are anti-mitotic drugs, meaning they arrest cell mitosis. Mitosis is the process by which cells divide and replicate. Taxanes have a different mechanism of action than other anti-mitotic drugs, such as the vinca alkaloids, because they bind to a different site on β -tubulin and promote rather than inhibit microtubule formation in cells (see Figure 3 below). By binding to the β -tubulin subunit of microtubules, they antagonize the disassembly of the key cytoskeletal protein, which results in bundles of microtubules and aberrant structures of microtubules in the mitotic phase of the cell cycle, which then leads to mitotic arrest.

Figure 3: Mechanism of Action of Taxanes



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann:
Goodman & Gilman's: The Pharmacological Basis of Therapeutics,
 Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

21. Reviews of the preclinical and clinical pharmacology of taxanes (*e.g.*, Pazdur *et al.* 1993; Gelman, 1994; Bissery *et al.* 1995; Cortes and Pazdur, 1995; van Oosterom and Schrlivers, 1995; Rowinsky, 1997; Michaud *et al.* 2000; Gligorov and Lotz, 2004; de Weger *et al.* 2014), include discussion of the similarities and differences between paclitaxel and docetaxel. Although both drugs are discussed as being able to bind to β -tubulin (Rowinsky, 1997; Wellstein *et al.* 2018. Cytotoxic drugs. In: *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13th edition.* Brunton *et al.* (eds.). New York, NY: McGraw-Hill, chapter 66), research has defined the effects of each drug more specifically. It is important to review the process of mitosis in order to understand the differences between the taxanes.

22. The process of mitosis is described in terms of the different phases in the life cycle of a cell. The cell cycle is divided into two stages known as mitosis and interphase. Mitosis, also referred to as the “M” phase of the cell cycle, is the stage before cell division that involves separation of chromosomes. Interphase is the stage after cells have completed mitosis and subsequent cell division, or cytokinesis. Thus, interphase is the period between mitoses. During interphase, cell growth and DNA replication occur in a series of orderly events in preparation for cell division. Most dividing cells double in size between one mitosis and the next. DNA is synthesized during only a portion of interphase. The first phase of interphase is known as the G1 phase; it is the interval between mitosis and initiation of DNA replication. During G1, the cell is metabolically active and continuously grows but does not replicate its DNA. The G1 phase during interphase is followed by the S phase (synthesis phase); DNA replication occurs during this phase. The completion of DNA synthesis is followed by the G2 phase, which is characterized by continued cell growth and synthesis of proteins involved in mitosis. In the case of docetaxel, its molecular mechanism differs from paclitaxel in that it has a higher affinity for β -tubulin and targets centromere organization and acting on cells in three of the cell cycle phases (S, G2 and M), while paclitaxel affects mitotic spindles in the G2 and M phases of the cell cycle (Gligorov and Lotz, 2004).

23. Both docetaxel and paclitaxel also induce apoptotic cell death *in vitro* in cancer cell lines, another potential mechanism that can contribute to the beneficial effects of these drugs, although docetaxel is much more potent than paclitaxel (Rowinsky, 1997; Haldar *et al.*

1997). Other differences between the two drugs that are discussed include the greater uptake of docetaxel into tumor cells and the slower efflux of the drug from these cells, leading to a longer time of retention of docetaxel within the tumor cell (Aapro, 1996; Gligorov and Lotz, 2004).

24. Even with these differences in molecular mechanism that appear to exist between docetaxel and paclitaxel, the benefits, or efficacy, of docetaxel and paclitaxel are similar in terms of treatment of breast cancer. For example, a comparison of the FDA-approved labeling for Taxol and Taxotere, where the efficacy of the drugs is described, shows that 1) both drugs have been approved for use in treatment of breast cancer after failure of prior chemotherapy, and 2) both drugs have been approved for use as adjuvant treatment in node positive breast cancer, where the drugs are used in combination with doxorubicin-containing chemotherapy (Taxol) and in combination with doxorubicin and cyclophosphamide (Taxotere). Both Taxotere and Taxol are listed in by the World Health Organization (WHO) as essential medicines for treatment of breast cancer. As the WHO document (WHO, 2010)⁴ states:

*“Both taxanes should be available for breast cancer treatment; since at the present, their use, based on available evidence, is different according to specific subgroups of patient and concomitant treatments associated. **However, their similarities prevail and could also be considered interchangeable to support a choice of either one or the other.**”*
[emphasis added]

Additionally, there are clinical guidelines that support the use of paclitaxel and docetaxel interchangeably (Arroyo *et al.* 2011). Thus, both docetaxel and paclitaxel, which have a similar chemical structure, and some differences in the underlying mechanism of action, are used by physicians to treat many types of cancer.

25. In addition to describing the mechanisms that underlie the pharmacodynamics, or beneficial effects, produced by docetaxel or paclitaxel, it is also important to understand the pharmacokinetics of the drug. In the simplest terms, pharmacokinetics is a description of what the body does to the drug, while pharmacodynamics is the study of what the drug does to the body. Pharmacokinetics involve the processes of absorption, distribution, metabolism and elimination of a drug. Taxanes, including docetaxel and paclitaxel, are administered by

⁴ http://www.who.int/selection_medicines/committees/expert/18/applications/8_submission_taxanes.pdf

intravenous injection, which means that there is direct delivery of the drug into the blood, bypassing the absorption barriers that exist with other routes of drug administration (*e.g.*, oral, inhalation, dermal, *etc.*). Thus, intravenous drugs are considered to be 100% bioavailable. Once delivered into the bloodstream, drugs distribute into cells and tissues of the body. In the case of some drugs, including docetaxel and paclitaxel, they are bound in blood to circulating proteins. Like all drugs, this protein-bound drug pool is unavailable for pharmacological activity; it is the free or unbound drug that has activity in cells. Like many drugs, docetaxel and paclitaxel are metabolized in the liver by enzymes that are part of the cytochrome P450 system before they are excreted, or cleared, from the body. Over 95% of the docetaxel or paclitaxel dose administered is excreted through the bile and feces.

26. The pharmacokinetics of docetaxel and paclitaxel are described in their labeling, and have been reviewed in the literature (*e.g.*, Sonnichsen and Relling, 1994; Kearns, 1997; Jabir *et al.* 2012; Kenmotsu and Tanigawara, 2015; Stage *et al.* 2018). Both docetaxel and paclitaxel exhibit a high level of inter-individual variability in pharmacokinetics (Mielke *et al.* 2007), and this level of variability affects the dosing of these drugs. In the case of docetaxel, pharmacokinetic analyses have shown that clearance of the drug from the body is affected by the level of α_1 -acid glycoprotein in blood (a protein that binds docetaxel), liver function, age and body surface area (Bruno *et al.* 1996); inter-individual differences in the way the drug is handled by the body has led to interest in pharmacogenetic screening and dose individualization for taxanes (Jabir *et al.* 2012).

27. Table 1 below summarizes some of the key pharmacokinetic parameters for docetaxel versus paclitaxel. Because of these pharmacokinetic differences that are apparent in clinical populations, it has been recommended that: “*We need to continue to work towards determining the optimal dose of docetaxel, taking into account individual patients’ status.*” (Kenmotsu and Tanigawara, 2015); and “*recent knowledge about interindividual variability and population modeling provides a novel scientific basis for an improved and individualized therapeutic approach [for paclitaxel].*” (Mielke, 2007). In the case of paclitaxel, newer formulations of the drug affect its pharmacokinetics, and ultimately drug efficacy and safety

(Stage *et al.* 2018). The pharmacokinetics of docetaxel and paclitaxel, therefore, are highly relevant to understanding the risks and benefits of these drugs.

TABLE 1 Summary and Comparison of Pharmacokinetic Parameters: Docetaxel versus Paclitaxel		
Parameter	Docetaxel	Paclitaxel
Modeling characteristics	Linear	Non-linear
Elimination half-life ($t_{1/2\beta}$)	13.6±6.1 hours	10-14 hours
Volume of distribution (V_d)	72±24 liters/m ² (not into CNS)	182 liters/m ² (not into CNS)
Plasma protein binding	94%	88-98%
Systemic clearance (Cl)	350 ml/min/m ²	300 ml/min/m ²
Renal excretion	2.1±0.2%	5±2%
Metabolic Factors	CYP3A4 and CYP3A5	CYP2C8, CYP3A4
Level of inter-individual variability	High	High

28. Inter-individual variability with Taxotere and Taxol pharmacokinetics is relatively high, resulting in differing results at various dosages (Andriguetti *et al.* 2017). As discussed by Andriguetti and colleagues (see page 3563): *“Treatment with these drugs has wide interindividual variability in the tolerability of adverse effects, caused by the individual differences in pharmacokinetics parameters, especially in clearance, which lead to large differences in exposure to the drug.” [emphasis added]* As a result, when the toxic effects produced by a drug are an extension of its pharmacology, a high level of inter-individual variability in pharmacokinetics would suggest that differences will be seen in the susceptibility of certain patients to toxicity. This general principle of pharmacology and toxicology is taught in textbooks and is known as dose-response, meaning that increases in exposure increase the likelihood that a drug will produce both beneficial effects and toxic effects, although toxicity is often dose-limiting (e.g., Aleksunes, L.M. 2019. Principles of toxicology. In: Casarett & Doull’s

Toxicology: The Basic Science of Poisons, 9th edition. C.D. Klaassen (ed.) McGraw-Hill: New York, chapter 2; Buxton, I.L.O. 2006. Pharmacokinetics and pharmacodynamics: the dynamics of drug absorption, distribution, action and elimination. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th edition. McGraw-Hill: New York, chapter 1).

29. The toxic effects of docetaxel and paclitaxel also are well documented and described in textbooks (e.g., Chabner *et al.* 2001. Chemotherapy of neoplastic diseases. In: *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 10th edition. Hardiman and Limbird (eds.). New York, NY: McGraw-Hill, chapter 52; Chabner *et al.* 2006. Antineoplastic agents. In: *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 11th edition. Brunton *et al.* (eds.). New York, NY: McGraw-Hill, chapter 51; Wellstein *et al.* 2018. Cytotoxic drugs. In: *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 13th edition. Brunton *et al.* (eds.). New York, NY: McGraw-Hill, chapter 66). The most common toxic effects linked to cytotoxic anti-neoplastic drugs, such as docetaxel and paclitaxel, include bone marrow suppression, gastrointestinal disturbances and hair loss, effects linked to direct toxicity to the rapidly dividing cells in these tissues (Trueb, 2009).

VI. Chemotherapy Induced Alopecia Versus Permanent, Irreversible Hair Loss

30. In this case, the toxicity of concern is permanent, irreversible hair loss, or permanent, irreversible alopecia. This toxicity is an injury or toxicity that means hair does not regrow. It is referred to in the medical and scientific literature at times as “CIPAL” or chemotherapy-induced permanent alopecia, and also as “PCIA” or permanent chemotherapy-induced alopecia (PCIA). Because it is a toxicity that results in lack of hair regrowth, permanent, irreversible hair loss is a different condition from chemotherapy-induced, or drug-induced, alopecia.

31. Alopecia (hair loss) is one of the most common toxic effects associated with use of anti-neoplastic drugs in humans. Chemotherapy-induced alopecia is normally reversible (Tosti *et al.* 1994; Trueb, 2009; Sample Informed Consent, Exhibit 2 of the Bassi deposition; Nurse Brochure, Exhibit 4 of the Bassi deposition; Investigator Brochure, Exhibit 7 of the Bassi deposition). This temporary alopecia typically induced by anti-neoplastic drugs is sometimes

referred to as “anagen effluvium”, which is the sudden, diffuse loss of anagen-phase, or growth-phase hair, that occurs within days to weeks of exposure to an anti-neoplastic drug. Anagen effluvium is more common and severe when there is a combination of anti-neoplastic agents employed. This is the concept of additivity in pharmacology and toxicology (Eaton and Gilbert, 2013), which occurs when more than one drug or chemical that have common toxic effects are given together.

32. Both docetaxel and paclitaxel use are known to cause reversible alopecia in patients (see FDA labeling for Taxotere and Taxol). The toxic effect of drugs like docetaxel that lead to hair loss include complete arrest of hair formation by direct toxic insult to the rapidly dividing cells in the hair follicle (Trueb, 2009). Such alopecia typically is seen within two to four weeks after treatment begins and hair regrowth is usually seen within six months of treatment ending (Tallon *et al.* 2010). Thus, in most cases, when drug therapy is completed, the drug is eliminated from the body and the hair will regrow. The lack of regrowth once drug exposure has ceased is what distinguishes permanent, irreversible alopecia, which is recognized in the medical literature as hair that fails to regrow or substantially regrow at least by six months after treatment has ended (Tallon *et al.* 2010; Namini *et al.* 2016; Kim *et al.* 2017; Kang *et al.* 2018). Although the general definition of hair loss still seen at six months after ending treatment is used in many studies, clinical evidence indicates that the lack of regrowth has been reported to persist for years (discussed below in more detail). Thus, the injury is not simply loss of hair but is failure of hair to regrow after drug exposure has ceased.

33. Although many anti-neoplastic drugs are associated with reversible hair loss during treatment, there is a difference in the propensity for the permanent, irreversible hair loss that has been linked to Taxotere use as compared to many other drugs. Reviews of the issue of irreversible alopecia generally describe it as a “rare” event with chemotherapy (Tallon *et al.* 2010). A review of the available data indicate that Taxotere has been associated with irreversible hair loss to a greater extent than other chemotherapeutic drugs, including Taxol (discussed below in more detail). In fact, the evidence linking Taxotere exposure with permanent, irreversible hair loss includes controlled clinical trial data as well as epidemiological data (case series) and

individual case reports. When the available evidence is considered, the weight-of-the-evidence indicates it is biologically plausible that Taxotere can cause CIPAL/ PCIA.

34. The first report of docetaxel-induced irreversible hair loss appeared in the scientific literature in 2001 (Nabholtz *et al.* 2001. *J. Clin. Oncol.* 19:314-321) and related to results from an investigator that was participating in a Taxotere clinical trial. Patients had been enrolled in a Phase II clinical study and the authors reported that the “*most common treatment-related chronic nonhematologic toxicity was alopecia (87%) with long-lasting (longer than 2 years) partial alopecia in four patients*” (see Nabholtz paper page 318; Sanofi_00217670). The percentage of patients at two years with irreversible alopecia was 4/54 or 7.4%; such a rate of occurrence would be considered common (frequent) based on definitions provided by the World Health Organization (WHO) for pharmacovigilance practices; WHO defines “very common” as a rate > 1 in 10, “common” (frequent) as a rate > 1 in 1000 but < 1 in 10, “uncommon” (infrequent) as a rate > 1 in 1000 but < 1 in 100, “rare” as a rate > 1 in 10,000 and < 1 in 1000, and “very rare” as a rate < 1 in 10,000⁵. Given that Dr. Nabholtz was an investigator for Sanofi (see page 331 of Gustavson deposition), this paper was of particular importance.

35. In 2006, a presentation at the San Antonio Breast Cancer Symposium by Dr. S.M. Sedlacek (Sedlacek, 2006) described clinical experience in treating breast cancer based on a retrospective review of patient data in his clinical practice. His report would be considered a type of epidemiological investigation. He reported that alopecia associated with docetaxel therapy as an adjuvant to doxorubicin/cyclophosphamide chemotherapy was irreversible in some patients (he called the condition “persistent significant alopecia” and abbreviated it as “PSA”). PSA rates reported for the three different treatment groups in his study were 6.3% in women administered doxorubicin plus Taxotere, 0% in women administered doxorubicin plus Taxol, and 0% in women administered doxorubicin without a taxane. Again, the rate of irreversible alopecia (PSA) reported by this physician would be considered a common adverse event in the Taxotere-treated group (consistent with WHO definitions). The rate of occurrence of irreversible alopecia in Taxotere-treated patients in this clinical population was higher as compared to Taxol and was not a rare event. The comparison of Taxotere experience with and without doxorubicin allows for

⁵ see http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf

consideration of the contribution of each drug independently to the risk in the patients. Taxotere use was associated with an increased risk of permanent, irreversible alopecia, a risk that was not seen with use of doxorubicin alone or with doxorubicin combined with Taxol use. Therefore, Taxotere carried an independent risk of CIPAL/ PCIA and was a substantial contributing factor to the condition in the women studied.

36. In 2009, Prevezas and colleagues described clinical experience in their dermatological practice with two patients that developed “*irreversible and severe alopecia*”; one woman had received Taxotere and letrozole, while the other woman had received Taxol only. The authors concluded with respect to the woman who had received Taxotere: “*We think that the irreversibility can be attributed only to the cytotoxic effect of docetaxel [Taxotere].*” These case reports of permanent, irreversible alopecia added to the evidence that began to accumulate starting in 2001.

37. Also, in 2009, a presentation was made at the San Antonio Breast Cancer Symposium by Dr. Hugues Bourgeois⁶. Dr. Bourgeois summarized data collected from 15 private institutions and public hospitals in France and reported that adjuvant chemotherapy⁷ can lead to persistent alopecia or suboptimal hair regrowth in patients. The investigators based their findings on case report forms for 82 patients (median age, 60 years) who received adjuvant treatment for breast cancer and were completed by physicians between May 2008 and October 2009 (also a type of epidemiological investigation). Irreversible alopecia was reported in all of the women. Dr. Bourgeois stated that he felt the 100 mg/m² dosage of Taxotere was “*too high*” as a recommended dosage and that he gives “*them [his patients] the choice [of] 4 courses of Taxotere with a [small percent chance] of permanent hair loss, or 12 weeks of Taxol with no risk of permanent hair loss. For the efficacy, it is the same.*”

38. In each of these papers and presentations reported through 2009, the authors were describing a new finding of irreversible or irreversible alopecia, that was different than the chemotherapy-induced alopecia that typically had been associated with taxanes previously, and

⁶ http://www.mdmag.com/journals/obtn/2010/march2010/sabcs_interview_series

⁷ Adjuvant chemotherapy is defined as additional cancer treatment after the primary treatment has been completed that is given to decrease the risk of cancer reoccurrence.

also appeared to be more common in Taxotere-treated patients. The authors attributed use of Taxotere to a type of hair loss that was different than the drug-induced alopecia that is linked to most chemotherapy drugs. When considered together, these papers provide evidence that it is biologically plausible that Taxotere can cause CIPAL/PCIA as well as providing evidence that CIPAL/ PCIA in patients receiving Taxotere is not rare.

39. In 2010, a literature review on chemotherapy-induced irreversible alopecia was published (Tallon *et al.* 2010). The authors also described a case of irreversible hair loss in a woman following standard dose chemotherapy with docetaxel, carboplatin and trastuzumab for breast cancer. The authors suggested that docetaxel was the causative agent in their patient. Important conclusions reached by the authors included the following:

- Chemotherapy-induced hair loss is typically considered completely reversible, but this is not always the case.
- Physicians and patients need to be aware of the rare possibility that alopecia following chemotherapy can be persistent.

40. In response to the publication by Tallon *et al.* (2010), a “*Letter to the Editor*” was published regarding this paper in 2013 (Tosti *et al.* 2013). Tosti and colleagues reported that five additional patients on docetaxel therapy had irreversible alopecia (Tosti *et al.* 2013). In their letter, the physicians stated: “*The real prevalence of this devastating long-term side effect of docetaxel is unknown, and efforts should be made to understand the mechanism of follicle destruction and to identify strategies for possible prevention.*” Yet, clinical data from docetaxel trials (Nabholtz *et al.* 2001; Sedlacek, 2006) had determined that irreversible alopecia was not a rare event in their clinical populations, a finding that is supported by the results of another Taxotere clinical trial known as TAX316 (discussed in detail below) where again the rate of CIPAL/ PCIA was not rare.

41. Two additional papers appeared in the scientific literature in 2011 describing docetaxel or paclitaxel use and irreversible alopecia (Miteva *et al.* 2011; Palamaras *et al.* 2011). Miteva and colleagues reported on ten cases of irreversible alopecia, six of whom had been treated with docetaxel (Miteva *et al.* 2011); the other patients in the case series included three

patients treated with busulfan for acute myelogenous leukemia, and one patient treated with cisplatin and etoposide for lung cancer. Notably, none of the women had a history of hair loss before chemotherapy treatment, and their hematological and endocrine assessment were all within normal ranges. The authors stated: *“Permanent alopecia after chemotherapy is unique for 2 reasons: (1) it is not reversible and (2) it is not cicatricial. In fact, the pathology shows lack of fibrosis and a preserved number of follicular units. This makes this condition very difficult to recognize under the microscope. It is likely that most pathologists would sign such cases as AGA if not provided with the clinical information.”* [see page 350 of Miteva et al. 2011] In the second paper, Palamaras and colleagues described a retrospective chart study of patients who had attended their dermatology practice for treatment of hair loss during the previous seven years. They compared their findings with reports identified by a literature search. Of the seven patients they found in their practice with persistent or irreversible alopecia, five were women that had been exposed to docetaxel (Taxotere) as part of a chemotherapeutic regimen while two other women had been exposed to busulphan. The authors also reported that on histopathologic examination, the patients scalp tissue showed “a marked reduction of follicular units with an increase in vellus hair formation and absence of any significant inflammation or scarring”, findings they stated were similar to those of Prevezas and colleagues where patients had been treated with taxanes.

42. In 2012, docetaxel-associated irreversible alopecia again was reported in patients being treated for breast cancer with taxanes (Bourgeois et al. 2012; Kluger et al. 2012). The publication by Bourgeois and colleagues is an abstract from the 35th annual meeting of the San Antonio Breast Cancer Symposium (2012) where the authors reported on cases of irreversible alopecia in a French database (ALOPERS). The database contained more than 100 patients with persisting alopecia and the authors stated that docetaxel was the drug linked with the adverse event in a majority of the patients. The authors concluded that docetaxel 75–100 mg/m² was the common agent in the majority of patients and that 43% of patients lacked hair regrowth more than 24 months after their last chemotherapy infusion. They also concluded: *“Optimal information of patients about alopecia and persisting alopecia appears to be mandatory before treatment: 47% of patients undergo a psychological shock during hair loss.”* They pointed to the results of a Taxotere clinical trial finding to support their conclusions. They stated: *“Moreover,*

BCIRG 001⁸ study (TAC versus FAC) led to the conclusion that docetaxel 75 mg/m² is responsible for persisting alopecia for 3% of patients. So, by extrapolating, in France, each year, docetaxel could induce a persisting alopecia in 300 patients.”

In the study by Kluger and colleagues (2012), the authors discussion was as follows:

“Women treated for breast cancer by a sequential adjuvant FEC and docetaxel regimen who developed permanent alopecia diagnosed between 2007 and 2011 were identified from the Department of Dermatology (Saint-Eloi Hospital, Montpellier, France) and the Department of Medical Oncology (CRLC Val d'Aurelle, Montpellier, France). Data were collected regarding demographics, type of cancer, delay of onset after chemotherapy, Dermatology Life Quality Index® (DLQI), clinical description of the lesions, scalp biopsies, laboratory explorations investigating steroid hormonal, iron, zinc and thyroid status, therapy and outcome. Twenty white Caucasian females were included. Hair loss presented with a moderate or intense androgenetic-like pattern of scalp alopecia. Biopsy specimen examinations were normal or displayed the androgeneticlike pattern. Laboratory explorations ruled out iron or zinc deficiency and thyroid disorders and confirmed hormonal menopause without hyperandrogenism. The overall mean DLQI score reflected the distressing psychological consequences in the patients' lives. No spontaneous regrowth of the scalp hair was noted. Treatment including vitamins, minoxidil, psoralen and ultraviolet A therapy and spironolactone proved to be ineffective. Permanent and severe alopecia is a newly reported complication of the FEC 100–docetaxel breast cancer regimen.”

Kluger and colleagues also concluded that the lack of complete hair regrowth was “probably” related to Taxotere use as an adjuvant drug in the regimen and estimated that the incidence of taxane-related CIPAL was about 2%, *i.e.*, not a rare event.

43. Docetaxel-associated irreversible alopecia has likewise been reported in the scientific literature since 2012 (*i.e.*, Bertrand *et al.* 2013; Martin *et al.* 2015; Sibaud *et al.* 2016; Namini, 2016; Kim *et al.* 2017; Fonia *et al.* 2017; Kang *et al.* 2018). Of these papers, several report incidences based on clinical data. For example, Namini (2016) reported that the clinical

⁸ This is TAX316 that is described below.

trial for docetaxel known as TAX316 results in an incidence of Taxotere-induced irreversible alopecia that was double that the comparator group (no Taxotere was included). In the 2016 review of dermatological adverse events with taxane therapy for cancer (Sibaud *et al.* 2016), the authors concluded:

“The hair loss in CIPAL [chemotherapy-induced permanent alopecia] is not total but rather relatively diffuse (111, 114), and tends to be accentuated in areas prone to androgenetic alopecia (115, 116, 118). The hair is finer and shorter (generally <10 cm) [114-116], but the scalp appears healthy, without features of cicatricial alopecia or fibrosis (figures 10 A-B) (111, 116). Hair at other sites (eyelashes, eyebrows, axillae, pubis, and body) can be affected as well (114, 116, 118). It is perceived that CIPAL is usually irreversible, but there are no long-term prospective studies confirming this, although the psychological impact can be substantial (115, 116, 119).”

The authors also addressed the issue of incidence of CIPAL in patients treated with taxanes. They stated:

“In the case of taxanes, Kluger et al. estimated the incidence to be 2% with docetaxel (116). However, findings of the French Drugs and Emerging Therapeutics Observatory (OMIT), and our personal experience, suggest that the incidence is higher and is likely underestimated (117).”

44. When the published literature is considered as a whole, in conjunction with Taxotere clinical trial data which will be discussed in more detail below, the weight-of-the-evidence indicates that it is biologically plausible that Taxotere can cause CIPAL/ PCIA when the drug is used as an adjuvant to treat early stage breast cancer, that the risk of permanent, irreversible alopecia is not rare, that Taxotere use carries an independent risk of CIPAL/ PCIA, and that Taxotere use is associated with an increased risk as compared to other drugs used in breast cancer treatment.

45. With respect to the issue of Taxotere use in breast cancer treatment and the fact that other drugs are typically administered along with Taxotere, it is important to consider the

evidence linking drugs used in combination with Taxotere with CIPAL/ PCIA (lack of hair regrowth). In this litigation, Sanofi's experts have suggested that cases of ongoing or irreversible alopecia have been reported for drugs other than Taxotere that included Taxol, cyclophosphamide, Adriamycin and 5-fluorouracil, as well as carboplatin, cisplatin, busulphan, melphalan, and thiotepa. In the case of each of these drugs, literature citations were identified⁹ as support for the expert to suggest that there is no evidence that Taxotere is an independent risk factor for permanent, irreversible alopecia (CIPAL/ PCIA). Yet, careful review of the literature¹⁰ cited to support this opinion is not the same type of evidence that exists for Taxotere and in some cases the authors of the papers failed to link the mentioned drug as the cause of a patient's irreversible hair loss.

46. For example, the drugs used most often in combination with Taxotere to treat early stage breast cancer include doxorubicin (Adriamycin®), cyclophosphamide (Cytoxin®) and 5-fluorouracil (5-FU). A review of the literature cited by Sanofi's experts to support the opinion that cases of permanent alopecia (PCIA) have been reported with other chemotherapy drugs only document case reports, not controlled clinical study data (discussed below) as is available for Taxotere. Additionally, in some cases, the authors of the cited references failed to specifically link the purported drug as causing CIPAL/ PCIA in the specific patient(s) considered (*e.g.*, for Adriamycin see Crown, 2017 and Yeager and Olsen, 2011; for carboplatin see de Jonge *et al.* 2002; for Taxol see Palamaras *et al.* 2011, Miteva *et al.* 2011 and Yeager *et al.* 2011).

47. Moreover, in the case of doxorubicin, as discussed above in paragraph 35, rates of CIPAL/ PCIA for the three different treatment groups in the Sedlacek (2006) study were reported to be 6.3% in women administered doxorubicin plus Taxotere, 0% in women administered doxorubicin plus Taxol, and 0% in women administered doxorubicin without a taxane. The comparison of Taxotere experience with and without doxorubicin allows for consideration of the contribution of each drug to the risk in the patients. Taxotere use was associated with an

⁹ Masidonski and Mahon, 2009; Crown, 2017; Yeager and Olsen, 2011; Jung and Lee, 2013; de Jonge *et al.* 2002; Miteva *et al.* 2011; Prevezas *et al.* 2009; Palamaras, 2011; Yang and Thai, 2015; Beisecker *et al.* 1997; Berglund *et al.* 1991; Tosti *et al.* 2005

¹⁰ Masidonski and Mahon, 2009; Crown, 2017; Yeager and Olsen, 2011; Jung and Lee, 2013; de Jonge *et al.* 2002; Miteva *et al.* 2011; Prevezas *et al.* 2009; Palamaras, 2011; Yang and Thai, 2015; Beisecker *et al.* 1997; Berglund *et al.* 1991; Tosti *et al.* 2005

increased risk of permanent, irreversible alopecia, a risk that was not seen with use of doxorubicin alone or with doxorubicin combined with Taxol use. Then, as discussed below, TAX316 provides evidence of an independent risk of CIPAL/ PCIA, and a higher risk, linked to Taxotere as compared with use of 5-fluorouracil.

48. Considering the evidence previously cited by Sanofi's experts, the suggestion that there is no significant evidence that Taxotere carries an independent risk of CIPAL/ PCIA is not scientifically defensible, particularly given the fact that the weight-of-the-evidence for Taxotere includes more than case reports alone.

49. In reviewing the scientific literature, it is important to understand that the biologic plausibility of the relationship of Taxotere to alopecia, including CIPAL/ PCIA is supported by preclinical testing data as well. In its initial preclinical testing with docetaxel, hair follicles were a target organ for toxicity in dogs and rats (Investigator's Brochure 1999, Exhibit 7 of the Bassi deposition).

50. As stated in the labeling for Taxotere, the mechanism of action of the drug as a cancer treatment is related to its ability to disrupt the microtubular network in cells that is essential for mitotic and interphase cellular functions; Taxotere inhibits mitotic activity in cells which are rapidly dividing (i.e., cancer cells; blood stem cells; cells in the hair follicles). As a result of the effects of Taxotere to inhibit cellular mitosis, drug-induced alopecia, specifically alopecia associated with cancer chemotherapy, is one of the most common cutaneous adverse effects observed in patients (Tosti *et al.* 1994). In the case of Taxotere, clinical studies have shown that alopecia occurred in over 90% of patients treated with the drug as an adjuvant therapy for breast cancer (*e.g.*, Martin *et al.* 2005) and in 75% of patients treated with docetaxel as the sole chemotherapeutic for metastatic breast cancer (see Taxotere labeling 1999). As discussed in the literature, combining chemotherapeutic drugs in treatment regimens can result in a higher incidence of alopecia as compared to situations when a drug is used as an individual therapy (Tosti *et al.* 1994). This observation also is consistent with general principles of pharmacology and toxicology where increased doses or exposure to a drug increase the likelihood of toxic effects (Eaton and Gilbert, 2013).

51. Sanofi identified docetaxel as a cause of irreversible alopecia (Sanofi_01101022; Sanofi_00829788; Sanofi_01827599; Sanofi_04876339; Sanofi_01268143¹¹). The company stated based on their review that: *“The cumulative weighted evidence is sufficient to support a causal association between Docetaxel and Permanent/Irreversible alopecia in patients who receive docetaxel.”* The information reviewed by Sanofi included the Sanofi pharmacovigilance database (adverse events reported to the company), two literature articles (Kluger *et al.* 2012 and Miteva *et al.* 2011) and two Taxotere clinical studies (TAX316 and GEICAM).

52. The issue of rate of occurrence of irreversible alopecia was addressed by FDA in 2015 (see the Medical Review dated December 7, 2015 by Tanya M. Prowell and Amy E. McKee). The FDA employees found from a review of the FDA’s adverse reporting database and the Sanofi pharmacovigilance database that 2,172 case reports of irreversible or lasting alopecia were identified in association with docetaxel use, and that the Taxotere labeling in 2015 did not reflect that alopecia could be irreversible. Further, FDA found that they, and the Sponsor (Sanofi) *“concur that the available evidence supports a potential causal association between docetaxel and permanent alopecia and that the label should be updated to alert clinicians and patients of this possibility”*.

53. It is interesting to note that the Company Core Data Sheet (CCDS) for Taxotere dated November 12, 2014 contained important information related to the permanence of Taxotere-induced alopecia that was not in the Taxotere labeling in 2014. The CCDS stated that the most common adverse events that persisted into a follow-up period with a median of over 10 years was alopecia (9.2% of patients) (see 2014 CCDS, Sanofi_01070281; CHMP Type II variation assessment report dated May 12, 2016).

54. A recent deposition of a Sanofi employee, Dr. Emanuel Palatinsky (see deposition dated August 9-10, 2018) provided testimony related to Taxotere that was informative. Dr. Palatinsky was global safety officer for Taxotere from May 2006 to December 2013. Documents showed that in 2011, the French regulatory authorities requested a safety assessment for

¹¹ Exhibit 6 to the Hangai deposition of February 1, 2018 (page 192)

irreversible alopecia in patients administered Taxotere (Exhibit 17). As part of that assessment the rapporteur concluded that *“Given the serious psychological consequences of this adverse effect in, often young, patients treated mainly in an adjuvant scheme, health care professionals and patients should be informed of the possible irreversibility of alopecia.”* When Dr. Palatinsky looked at the issue of rate of occurrence of irreversible alopecia based on Sanofi’s own data the results showed that from 3% to 6% of patients had experienced irreversible alopecia (Exhibit 26).

55. A review of the deposition of another Sanofi employee, Dr. Linda Gustavson (dated May 3, 2018) also provided important information related to the issue of irreversible alopecia and Taxotere. Dr. Gustavson worked in global regulatory affairs at Sanofi from 2004 until November of 2010. Documents discussed during her deposition showed that Sanofi should have been aware of the risk based on information from the published literature and their own clinical data (TAX316; GEICAM). In addition, French regulatory authorities raised concerns regarding Taxotere related to irreversible alopecia in 2010 (Exhibit 19) and the findings were stated by the French as follows:

A total of 17 cases of irreversible alopecia following breast cancer chemotherapy are recorded in the National Pharmacovigilance database and there are two published cases. Analysis of the national pharmacovigilance database reveals that persistent alopecia has only been reported since the year 2000, that they are only described for breast cancer treatment and that docetaxel is a common feature of the great majority of the cases involving chemotherapy.

56. The deposition of Sanofi employee Kimberly Bassi was reviewed as well (dated August 10, 2018). A review of the documents and information that were discussed in the deposition were relevant to the issue of irreversible alopecia with Taxotere treatment with respect to what was known by the company over time. Exhibit 5 of the Bassi deposition shows that Sanofi was aware that alopecia with Taxotere treatment did not reverse in all cases. Exhibit 9 of the Bassi deposition shows that Sanofi had received an adverse event report on a patient in TAX316 in 2003 where the patient had unresolved alopecia or irreversible alopecia and the patient was now 5 years and 5 months out from treatment with Taxotere. Additionally, at that

time the investigator reporting the event identified it as “*serious*”. In that same exhibit (Exhibit 9) another adverse event had been reported in July 2000 where a patient had irreversible alopecia and the investigator had identified the event as “*serious*” (see page 253 of the deposition). In 2000 as well, Sanofi was made aware of another case of irreversible or permanent alopecia in a patient treated with Taxotere as part of a clinical trial where the alopecia was again listed as a serious event by the investigator (Dr. Nabholtz). By 2008, Sanofi was aware that the rate of persistent or irreversible alopecia in TAX316 in TAC patients (Taxotere group) was double the rate in the FAC group (see page 306-309). Then, by 2013, Sanofi knew that the rate of persistent or irreversible alopecia in the TAC group of TAX316 was 3.9%, while the rate was even higher (6.7%) in the GEICAM study (Exhibit 23; corrected percentages found in CHMP Type II variation assessment report dated May 12, 2016). These clinical studies provide important evidence to support the biologically plausible relationship between Taxotere and CIPAL/ PCIA and the fact that Taxotere carries an independent risk of CIPAL/ PCIA, as well as indicating that Taxotere poses an increased risk of CIPAL/ PCIA as compared to other drugs. Although these studies involved combination drug treatment, the study design allows for isolation of the increase in risk linked to Taxotere use; the difference when TAC and FAC groups are compared is the substitution of Taxotere for 5-fluorouracil (5-FU). Therefore, Taxotere was a substantial contributing factor in terms of increasing the risk of CIPAL/ PCIA in these patients.

57. Thus, it is clear that at least two clinical studies performed by Sanofi with Taxotere provided important information concerning irreversible alopecia (TAX316 and GEICAM). TAX316 was a phase III clinical study of Taxotere in node-positive breast cancer patients where Taxotere was used as an adjuvant in combination with doxorubicin and cyclophosphamide (TAC group) as compared to patients receiving 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC group) (Exhibit 3 from the Gustavson deposition). Phase III clinical trials are the most important studies in terms of demonstrating both efficacy and safety of drugs. The study began in 1997 and continued until 2010, for a total of 10 years of follow-up on patients. An interim analysis of the study was performed after 5 years as well (2004). As already mentioned, the results at 10 years showed that 3.9% of patients in the TAC group had unresolved or irreversible alopecia while 2.2% of patients in the FAC group had unresolved or irreversible alopecia; Taxotere-treated patients were nearly twice as likely to

experience irreversible alopecia. Based on this study alone, Taxotere use in the TAC treatment regimen had been shown to more likely associated with irreversible alopecia than patients exposed to FAC treatment, no Taxotere included. GEICAM was a similar Phase III study but the patients were node-negative breast cancer patients. In GEICAM, the rate of irreversible alopecia was originally reported as 6.7% in the TAC group. However, there were serious problems with the follow-up of patients in this study and that percentage of 6.7% originally reported was derived from only 49 study subjects that had alopecia that persisted into the follow up period and represented events from only 12 of 55 study sites. The remaining 43 study sites reported no study subjects with alopecia that persisted into the follow up period, which is suspect given the known toxicities of this drug. It also demonstrates that neither the 6.7% originally reported, nor the 0.6% reported based on the n=532 in the TAC arm of TAX301 that was later reported, can be seen as an accurate value that can be applied to all sites. Yet, even if 6.7% is not representative of all sites, the data, when considered in conjunction with data from TAX316 provides important evidence that irreversible alopecia is not a rare event with Taxotere use in women.

58. In another clinical study performed by Sanofi (TAX311), the company stated that this study was “*the first and only study to directly compare Taxotere and Taxol as single agent chemotherapy for the treatment of metastatic breast cancer (MBC)*” (Sanofi_05656089). Given the issue of interchanging one taxane for another, the data in this study were informative in terms of the comparative toxicity of paclitaxel and docetaxel. It is interesting to note that this clinical study was performed as part of a post-approval commitment to FDA due to concerns about Taxotere toxicity (see Sanofi_03319024, which was Exhibit 3 to the deposition testimony of Vanina Groult). A review of the Clinical Study Report for TAX311 (Sanofi_205617796) showed that Taxotere and Taxol did not exhibit the same toxicity profile in this study where the only drugs used were Taxol or Taxotere (no combination therapy). It should be noted that the dose of Taxol used (175 mg/m²) was higher than a dose shown to have similar efficacy in a phase III study of metastatic breast cancer as single drug therapy (see Taxol labeling 2010). This is important because the use of a higher dose of Taxol would be expected to result greater toxicity, and in a greater likelihood of patients experiencing an adverse event. Yet, the data showed that taxane-induced deaths only occurred in the Taxotere study group (four deaths were attributed to Taxotere while no deaths were attributed to Taxol; see page 7). In fact, Taxotere administration

was associated with more drug-induced deaths and a greater rate of both non-serious and serious adverse events (see pages 78 and 134). Although this study did not provide data on the persistence of alopecia in either study arm, the clear differences in Taxotere-related toxicity as compared to Taxol treatment are important when comparing the toxicity profiles of the two drugs. The small size of the study in terms of number of patients included in each group do not provide sufficient support for making any labeling or promotional claims about clinical superiority, even though the study showed that there were statistically significant differences in some efficacy outcomes related to anthracycline-resistant breast cancer (see 2009 DDMAC letter). The significant increase in toxicity seen in Taxotere-treated patients also must be weighed. It should also be noted, that the administration of paclitaxel in this study was every 3 weeks and not weekly as is generally done, and there has been no head-to-head study where paclitaxel is administered weekly. In order to demonstrate superiority in efficacy, a much larger Phase II study would need to be performed.

59. Another study directly comparing Taxol and Taxotere safety and efficacy has been published where the taxanes were used as an adjuvant treatment for breast cancer has been published (Sparano *et al.* 2008). The investigators enrolled 4950 women with axillary lymph node-positive or high-risk, lymph node-negative breast cancer. All patients first received four cycles of intravenous doxorubicin and cyclophosphamide every three weeks and were then assigned to intravenous paclitaxel or docetaxel given every three weeks for four cycles, or once a week for twelve cycles. Both safety and efficacy endpoints were reported for each treatment group. The authors reported that patients treated with Taxotere were more likely to experience certain types of toxic effects (*i.e.*, neutropenia and infection) as compared to patients receiving Taxol. Although alopecia was common in both Taxol and Taxotere treatment groups, the authors did not provide data on the persistence of alopecia. Taxol was shown to be superior to Taxotere on overall survival in the study (five-year survival) when weekly Taxol was compared to Taxotere given either weekly or every three weeks; the drugs were not different in terms of disease-free survival (five year).

60. When considering the efficacy and safety of an anti-neoplastic drug, it is important to remember that in many cases drugs are used in combination. In the case of docetaxel, FDA-approved indications include combination therapy with doxorubicin,

cyclophosphamide, prednisone, cisplatin and/or fluorouracil. Prednisone is an immunosuppressant drug that is used to treat a variety of disease linked to activity of the immune system (*i.e.*, allergies, autoimmune diseases, *etc.*), including some types of cancer. Prednisone itself is not associated with alopecia (see FDA labeling for prednisone drug products).¹² Cisplatin is rarely associated with alopecia (Trueb, 2009; FDA-labeling¹³), while fluorouracil is reported to be associated with alopecia (Trueb, 2009; see FDA labeling).¹⁴ Doxorubicin and cyclophosphamide also are often associated with alopecia (Trueb, 2009; see FDA labeling¹⁵). A review of the published scientific literature shows that although there are some case reports of CIPAL/ PCIA with other chemotherapy drugs, the case reports are far fewer than the reports linked to Taxotere and the available evidence does not include controlled clinical studies such as the studies available for Taxotere.

61. Further, as discussed above, although cases of irreversible alopecia have been reported with Taxol use, the reports in the medical literature with Taxotere use have been much more frequent (*e.g.*, Sedlacek, 2006; Prevazas *et al.* 2009; Chow *et al.* 2013), and clinical trial data is available only for Taxotere. Moreover, although the scientific literature has suggested that high dose use of docetaxel is more likely associated with irreversible alopecia (Bourgeois, 2014; Crown, 2017; Martin, 2018), individual cases of CIPAL/ PCIA have occurred with use of lower dose Taxotere regimens as well (less than 400 mg/m²; *e.g.*, Martin *et al.* 2018; Kluger *et al.* 2012; Sedlacek, 2006). Therefore, there is variability in the cumulative doses of Taxotere that have been linked to CIPAL/ PCIA in patients where Taxotere has been administered as an adjuvant treatment for early stage breast cancer. This is not surprising given the high inter-individual variability in Taxotere pharmacokinetics which would affect drug exposure levels in patients (see paragraph 27 above; Andriguetti *et al.* 2017). As a result, in any one individual patient, it is exposure to Taxotere that puts the patient at increased risk of CIPAL/ PCIA, a risk that would not be absent if lower doses of the drug were used. Although a threshold for risk may

¹² *e.g.*, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021959s004lbl.pdf

¹³ *e.g.*, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018057s079lbl.pdf

¹⁴ *e.g.*, https://www.accessdata.fda.gov/drugsatfda_docs/anda/2000/40334_Fluorouracil_Prntlbl.pdf ;
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/012209s040lbl.pdf

¹⁵ https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050718s029lbl.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050467s070lbl.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf

exist, studies have not been performed, by Sanofi or others, that identify a level of Taxotere exposure that would be without risk of CIPAL/ PCIA.

VII. Conclusions

62. Based on my review of scientific literature, clinical study reports, documents submitted to FDA, and my knowledge and experience as a pharmacologist and toxicologist, it is my opinion to a reasonable degree of scientific certainty that Taxotere is more toxic than Taxol. It also is my opinion that irreversible alopecia (CIPAL/ PCIA) is not the same as drug-induced alopecia, a condition that is commonly seen with anti-neoplastic drug use. CIPAL/ PCIA is a condition where hair fails to regrow, or substantially regrow after exposure to the drug has ceased. Moreover, available evidence indicates that: 1) Taxotere use is associated with a greater risk of CIPAL/ PCIA as compared to some other anti-neoplastic drug products, including Taxol; 2) it is biologically plausible that Taxotere exposure can cause CIPAL/ PCIA; 3) Taxotere carries an independent risk of CIPAL/ PCIA; and 4) when used in combination, Taxotere has been a substantial contributing factor to CIPAL/ PCIA. I reserve the right to supplement these opinions if additional information becomes available.

VIII. Compensation

63. My compensation by plaintiff's attorneys in this matter is at the rate of \$300.00 per hour.



Laura M. Plunkett, Ph.D., DABT

EXHIBIT I

Filed Under Seal

EXHIBIT I

SUPPLEMENTAL EXPERT REPORT

DAVID A. KESSLER, M.D.

I. Background

1. Except as stated herein, for purposes of this Supplemental Expert Report (“Supplement”), I incorporate my Expert Report dated November 6, 2018 (“November 2018 Report”) as if fully set forth herein.

2. My understanding is that the bellwether plaintiffs at this time include but are not limited to: 1) Cynthia Thibodeaux v. Sanofi S.A., et al., Case No. 2:16-cv-15859; and 2) Sheila Crayton v. Sanofi S.A., et al., Case No. 2:17-cv-05923.¹ Both of these plaintiffs were administered Taxotere in 2008.

II. Supplement of Opinions in November 2018 Report.

A. Opinions Regarding Sanofi’s Duty to Warn Physicians and Patients About the Risk of Irreversible Alopecia Associated With Taxotere as of 2008.

3. Based on the reasons set forth in my November 2018 Report, as supplemented herein,² I conclude that my opinions regarding Sanofi’s duties as of 2008 are the same as those provided in my November 2018 Report.³

4. My opinion is that based on all scientific evidence, Sanofi should have warned patients and physicians about the risk of irreversible alopecia with Taxotere in its label by as early as 2006, and certainly by 2008. This is consistent with my prior testimony.⁴

¹ An updated Schedule 2, MDL Bellwether Cases, is attached to this Supplement.

² As noted in paragraph 11 and footnote 5 of my November 2018 Report, I reserved the right to review additional documents or information. For purposes of this Supplement, I have reviewed additional documents and information set forth in Supplemental Appendix C.

³ As noted in paragraph 11 and footnote 5 of my November 2018 Report, I reserved the right to analyze the issues at both earlier and later dates.

⁴ See Deposition of Dr. David Kessler, December 20, 2018 at 250:17-252:1; Trial Testimony of Dr. David Kessler, September 17, 2019 at 331:3-10, 386:24-387:2, 434:2-8.

B. Clarification Regarding What Section of the Taxotere Label Sanofi Should Have Warned.

5. For clarification regarding what section of the label Sanofi should have warned patients and physicians about the risk of irreversible alopecia with Taxotere by as early as 2006, and certainly by 2008, my opinion is that based on all scientific evidence, Sanofi should have clearly and prominently warned patients and physicians about the risk of irreversible alopecia with Taxotere or Taxotere-containing regimens in its label.

6. I have concluded that the available scientific evidence warranted Sanofi providing patients and physicians with a Warning regarding irreversible alopecia with Taxotere.

7. I have also concluded that the available scientific evidence warranted Sanofi advising patients and physicians about the risk of irreversible alopecia with Taxotere in other sections of the label, including the Adverse Reactions section.

7.1. As set forth in paragraph 66 and footnote 66 of my November 2018 Report, the standard for advising patients in the Adverse Reactions section of the label concerns “those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.”⁵

7.2. In my opinion, the available scientific evidence cited in my November 2018 Report provided “some basis to believe there is a causal relationship” between Taxotere and irreversible alopecia.

7.3. The standard for advising patients in the Adverse Reactions section further states that “additional detail about the nature, frequency, and severity of the adverse reaction and

⁵ See 71 Fed. Reg. 3922-3997 (January 24, 2006) at 3990.

the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.”⁶

7.4. The FDA’s 2006 Guidance for Industry on “Adverse Reactions Section for Labeling for Human Prescription Drug and Biological Products” cited in paragraph 101.1 and footnote 110 of my November 2018 Report states “[t]o the extent information is available and relevant, additional detail about the nature, frequency, severity, duration, dose-response, and demographic characteristics of those adverse reactions with significant clinical implications.”⁷

7.5. In addition, the standard for advising patients in the Adverse Reactions section states that the list of adverse reactions “must be preceded by the information necessary to interpret the adverse reactions.”⁸

7.6. In my opinion, because irreversible alopecia has significant clinical implications and information about irreversible alopecia with Taxotere was available, relevant, and important, Sanofi should have provided patients and physicians the information necessary to interpret the alopecia with Taxotere, including additional detail about the nature, frequency, severity and duration of alopecia with Taxotere.

7.7. Sanofi’s statement in its label listing only “alopecia” or, in certain labels, that “hair generally grows back”, was misleading when there was available and relevant information about the nature, frequency and duration of irreversible alopecia with Taxotere.

⁶ This standard is also set forth in the FDA’s 2006 Guidance for Industry on “Adverse Reactions Section for Labeling for Human Prescription Drug and Biological Products”, which is cited in paragraph 101.1 and footnote 110 of my November 2018 Report (“To the extent information is available and relevant, additional detail about the nature, frequency, severity, duration, dose-response, and demographic characteristics of those adverse reactions with significant clinical implications.”) (citing 21 CFR § 201.57(c)(7)(ii)(A)).

⁷ See FDA Guidance for Industry: Adverse Reactions Section for Labeling for Human Prescription Drug and Biological Products – (Jan. 2006) (citing 21 CFR § 201.57(c)(7)(ii)(A)).

⁸ 21 CFR § 201.57(c)(7)(i), (ii)(B); see also FDA’s 2006 Guidance for Industry on “Adverse Reactions Section for Labeling for Human Prescription Drug and Biological Products.

These statements in the label did not provide the information necessary to interpret irreversible alopecia with Taxotere.

7.8. Sanofi's Taxotere labeling in 2008 and continuing through 2019 included statements regarding the nature, frequency and duration of adverse reactions experienced with Taxotere and/or Taxotere-containing regimens (including TAC) other than irreversible alopecia.⁹

III. Supplemental Opinion on General Causation.

8. During both my prior deposition and trial testimony in the Taxotere litigation, Sanofi raised the question of whether I was providing an opinion on general causation.¹⁰ I testified during both my prior deposition and trial testimony in this Taxotere litigation that, although there is an interplay between the "reasonable evidence of a causal association" standard from a regulatory perspective and the standard for analyzing general causation, I was not at that time providing an opinion on general causation.¹¹

9. Utilizing my education, training and skill in the fields of epidemiology and biostatistics, and my experience of more than 40 years studying pharmacoepidemiology and the causal relationship between adverse events and drugs, I have now reviewed and analyzed the weight of the evidence to determine whether there is a causal relationship between Taxotere and irreversible alopecia. To be clear, although I am analyzing some of the same evidence from my November 2018 Report, I am now providing an additional opinion regarding general causation in this Supplement.

⁹ See, e.g., 2008 and 2019 Taxotere labels.

¹⁰ See Deposition of Dr. David Kessler, December 20, 2018 at 268:18-270:15; Trial Testimony of Dr. David Kessler, September 17, 2019 at 398:3-14.

¹¹ *Id.*

10. This general causation opinion reviews and analyzes two issues: (i) whether there is a statistically significant increased risk of irreversible alopecia with Taxotere; and (ii) application of the Bradford Hill criteria.

A. Evidence of a Statistically Significant Increased Risk of Irreversible Alopecia With Taxotere.

11. In order to determine whether there is evidence of a statistically significant increased risk of irreversible alopecia with Taxotere, I first identified, reviewed and analyzed the following data sources: (i) Sanofi's TAX 316 and TAX 301 clinical trial data; (ii) reports of irreversible alopecia in Sanofi's internal global pharmacovigilance database; (iii) a statistical analysis of the FDA's Adverse Event Reporting System database; (iv) medical literature discussing or identifying reports of irreversible alopecia after treatment with Taxotere, Taxotere-containing regimens, or other chemotherapy drugs; (v) Sanofi's internal documents; and (vi) Sanofi's communications with and submissions to U.S. and foreign regulatory authorities.

12. In the regular course of my training and experience, I routinely request biostatisticians to provide statistical calculations of scientific data and evidence for my review. In my November 2018 Report, I discussed certain statistical calculations performed upon my request by Dr. David Madigan that I reviewed and agreed with. I incorporate that discussion and analysis from my November 2018 Report herein.

13. Specifically, in my November 2018 Report, I discussed statistical analysis comparing the adverse event rate for irreversible alopecia in the TAC versus FAC arms from the TAX 316 and TAX 301 clinical trials that demonstrated a statistically significant increased risk of irreversible alopecia for patients in the TAC arm versus the FAC arm at nearly all time

periods in the TAX 316 clinical trial.¹² I have seen no evidence that Sanofi conducted any statistical analysis comparing the risk of irreversible alopecia in the TAC versus FAC arms of either the TAX 316 or TAX 301 clinical trials at any other time.¹³

14. Moreover, a pooled analysis (random effects meta-analysis) of the adverse event rates for irreversible alopecia from the TAX 316 and TAX 301 clinical trials demonstrated a statistically significant increased risk of irreversible alopecia for patients in the TAC arm versus the FAC arm (a rate ratio of 1.85 with a corresponding 95% confidence interval (1.04, 3.31) and a p-value of 0.04).¹⁴

¹² The risk ratio of irreversible alopecia for patients in the TAC arm versus the FAC at the 2009 final time period for the TAX 316 clinical trial is 1.80, 95% confidence interval (0.98, 3.28). (*See* November 2018 Report). Nevertheless, based on my review, the incidence rate for irreversible alopecia in both GEICAM 9805/TAX 301 and TAX 316 may be under reported. *See id.*

The number of subjects followed into the follow-up period for GEICAM 9805/TAX 301 was only 49/532 (9.2%). *See* TAX 301/GEICAM 9805 Interim Clinical Study Report, Jan. 30, 2004 (Sanofi_00799397); TAX 301/GEICAM 9805 Clinical Study Report, Nov. 9, 2009 (Sanofi_00799597). As Sanofi states, the final clinical trial report for GEICAM 9805/TAX 301 states “during 5 year follow-up, the CSR [clinical trial report] notes ‘Most TEAEs were followed into the follow-up period at the discretion of the Investigator.’ This implies that the most of cases of alopecia were not followed during the follow up period in the GEICAM study.” Nanae Hangai, Docetaxel Labeling Queries from PMDA [Japan’s Pharmaceutical and Medical Devices Agency], May 24, 2016 (Sanofi_01331114).

For TAX 316, Sanofi states that its follow-up reporting and collection strategy did not include capturing adverse event start and stop dates to fully understand the duration of adverse events like irreversible alopecia. *See, e.g.*, Email from Jean-Philippe Aussel to Catherine Crane and Michael Kopreski, May 21, 2012 (Sanofi_02932469) (“I confirm also that the CRF AE modules did not capture AE start and stop dates Note for very large adjuvant trials conducted on product with a well known safety profile (here Taxotere) and in which AE durations are not analyzed, the collection of AE start and stop dates would have yielded only extra validation, queries etc for no added value in terms of safety results. FYI-similar AE collection strategy (without dates) was applied for the TAX-316/BCIRG-001 early breast cancer pivotal registration study without any consequences on the positive outcomes of the FDA/EMA approvals.”).

¹³ *See also* Deposition of Barry Childs, M.D., October 26, 2018 at 113:23-114:9 (“Q. Do you know whether Sanofi ever engaged in any clinical trials to determine whether or not Taxotere can cause permanent hair loss in some people who are administered the drug? A. I’m not aware that Sanofi did that, and I certainly was not part of anything that they did with respect to that.”) (objection omitted). I also reviewed Sanofi’s internal Summary of Clinical Pharmacology Information and the deposition testimony of Dr. Paul Chew and accompanying exhibits. Based on this evidence, 221 of 1,024 studies performed by Sanofi were lost or destroyed. Of these 221 studies, 49 were Taxotere studies.

¹⁴ *See* November 2018 Report.

15. In addition to the statistical calculations analyzed in my November 2018 Report, for purposes of my general causation opinion, I requested that Dr. Madigan perform certain additional statistical calculations of the evidence I identified and reviewed.¹⁵

16. Specifically, I requested statistical calculations regarding: 1) data reported by Sanofi from its clinical trial studies TAX 316 and TAX 301 at different points in time, 2) data from certain studies in the medical literature that compared irreversible alopecia with Taxotere versus other comparator drugs; and 3) a logistic regression analysis of data from the FAERS database.

17. I requested that statistical analyses be performed of Safety Update Reports regarding the TAX 316 clinical trial prepared by Sanofi as part of Sanofi's ongoing obligations in Europe.¹⁶ These statistical calculations were based on the number of patients with irreversible alopecia reported annually by Sanofi in these reports from 2004 through 2009.¹⁷

18. The statistical analysis demonstrates a statistically significant increased risk of irreversible alopecia for patients in the TAC arm versus the FAC arm in each year being reported by Sanofi from TAX 316 (a rate ratio of 2.60).¹⁸

19. A random effects meta-analysis combining the results of TAX 301 annually demonstrated that the results were also statistically significant each year (a rate ratio of 2.63).¹⁹

¹⁵ To the extent any of the additional statistical calculations discussed herein are based on evidence available as of 2008, such evidence also supports the regulatory opinions provided in my November 2018 Report, as supplemented and clarified in this Supplement

¹⁶ Expert Report of David Madigan, Ph.D., dated October 20, 2019 at 23-26 ("Madigan October 2019 Report"); *see also* Sanofi_01294774 (2005 Safety Update Report); Sanofi_05956179 (2006 Safety Update Report).; Sanofi_04014414 (2007 Safety Update Report); Sanofi_03929385 (2008 Safety Update Report). Sanofi_03935020 (2009 Safety Update Report); Sanofi_01294924 (2006 Rapporteur Assessment Report).

¹⁷ Madigan October 2019 Report at 23-26.

¹⁸ *Id.*

¹⁹ *Id.*

20. A statistical analysis of the only four studies in the medical literature identifying original reports that presented an analysis of novel patient data comparing docetaxel to other cancer drugs in relation to irreversible alopecia demonstrated that three of the studies yielded a statistically significant increased risk of irreversible alopecia for patients administered docetaxel.²⁰

21. A meta-analysis of the four studies yielded an odds ratio of 4.13 with a 95% confidence interval (1.44, 11.81) and a p-value of 0.008.²¹

22. A logistic regression analysis of results from the FAERS database comparing docetaxel versus comparator drugs demonstrated that docetaxel became statistically significant compared to the other drugs in 2003 and remained statistically significant through 2017.²²

23. I have reviewed and agree with the requested statistical analysis and calculations in my November 2018 Report and this Supplement.

²⁰ *Id.* at 22-23 (citing to Crown, J., Incidence of permanent alopecia following adjuvant chemotherapy in women with early stage breast cancer, *Annals of Oncology*, 28 (2017, suppl_5); Kang, D., Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study, *The Oncologist*, (2019, 24(3) at 414-420); Martín, M., Persistent major alopecia following adjuvant docetaxel for breast cancer: incidence, characteristics, and prevention with scalp cooling, *Breast Cancer Research and Treatment*, (2018, 171(3) 627-634, at 635-636); Sedlacek, S., Persistent significant alopecia (PSA) from adjuvant docetaxel after doxorubicin/cyclophosphamide (AC) chemotherapy in women with breast cancer. *Breast Cancer Research and Treatment*, (2006, 100); noting statistically significant results in Kang, Martin, and Sedlacek studies).

The statistical analysis demonstrated that Crown (odds ratio 1.37, $p=0.80$), Sedlacek (odds ratio 54.7, $p=2.6 \times 10^{-5}$) and Martin (odds ratio 3.61, $p=1.2 \times 10^{-8}$) were all statistically significant. The fourth study, Kang, did not provide data regarding the number of patients receiving each regimen, but did provide an odds ratio comparing docetaxel to non-docetaxel treatment regimens of 8.01 (95% confidence interval 1.20-53.26).

²¹ *Id.* Dr. Madigan noted that there is significant between-study heterogeneity, $I^2=62.9\%$, although not statistically significant.

²² *Id.* at 16-19. Dr. Madigan also included methotrexate, gemcitabine and bevacizumab amongst the comparative drugs studied. The results for this comparator do not change my analysis or opinions. In 2003, the analysis yielded an odds ratio for docetaxel of 2.96, with a 95% confidence interval (1.30, 6.73). By 2017, the analysis yielded an odds ratio for docetaxel of 6.74, with a 95% confidence interval (5.24, 8.67). Docetaxel was the only study drug that was statistically significant as of the end of 2017. As of 2008, docetaxel was the only study drug ever demonstrating a statistically significant increased risk. As of 2008, the analysis yielded an odds ratio of 2.55, with a 95% confidence interval (1.31, 4.95). From 2012 through 2016, 5-fluorouracil was also statistically significant, though at a considerably lower odds ratio than docetaxel (e.g., in 2012, the odds ratio for docetaxel was 7.53 versus 2.34 for 5-fluorouracil).

24. Based on my identification, review, and analysis of the available scientific evidence, my review of the requested statistical analysis and calculations, and my experience, training, and education, there is evidence of a statistically significant increased risk of irreversible alopecia with Taxotere.

B. Application of the Bradford Hill Criteria.

25. In his seminal 1965 article “The Environment and Disease: Association or Causation?” Sir Austin Bradford Hill laid out nine “aspects of [an] association” to consider in determining whether the association is causal, now often referred to in pharmacoepidemiology as the Bradford Hill factors or criteria.²³ The complete list of the nine Bradford Hill factors is as follows: (1) strength of the association; (2) consistency (whether the association has been repeatedly observed “by different persons, in different places, circumstances and times”); (3) specificity (whether there are alternative causes of a condition); (4) temporality (whether the condition followed the exposure to the agent); (5) biological gradient (whether a dose-response relationship exists); (6) plausibility (whether the association is biologically plausible); (7) coherence (whether the association “seriously conflict[s] with the generally known facts of the natural history and biology of the disease”); (8) experiment (whether the condition improves upon removal of the hypothesized causative agent); and (9) analogy.²⁴

²³ Hill, Austin Bradford (1965). “The Environment and Disease: Association or Causation?” *Proceedings of the Royal Society of Medicine*. 58(5): 295-300. PMC 1898525.

²⁴ *See id.* In my November 2018 Report, I analyzed whether there is reasonable evidence of a causal association between Taxotere and irreversible alopecia by assessing the seven factors set forth in the 2011 FDA Guidance. As I noted in my November 2018 Report, the epidemiological literature has utilized many of these factors in assessing the relationship between a drug and an adverse event for decades also.

26. No one Bradford Hill factor is determinative, and a causal relationship does not require satisfaction of all nine factors.²⁵

27. To determine whether this is a causal relationship between Taxotere and irreversible alopecia, I have applied the Bradford Hill criteria to the available evidence, including the evidence cited in my November 2018 Report and the additional evidence set forth in this Supplement, including Supplemental Appendix C.

28. Because many of the factors overlap with the factors from the FDA Guidance, I incorporate herein my analysis of those factors and the evidence relevant to my assessment of those factors from my November 2018 Report. However, for purposes of my epidemiological opinions in this Supplement, my analysis of the Bradford-Hill criteria is not limited to evidence available as of 2008 or any other particular timeframe.²⁶

29. Below is an analysis of the key evidence supporting my application of each Bradford-Hill criteria.

i. Strength of Association

30. The Bradford Hill Criteria for strength of association is similar to the FDA Guidance factor for controlled trial group analysis. I incorporate my discussion of this factor from my November 2018 Report herein.²⁷

31. The contemporary application of this fact looks not only at the magnitude of association but also the statistical significance of the association. Even weak associations can be

²⁵ Hill, Austin Bradford (1965). "The Environment and Disease: Association or Causation?" Proceedings of the Royal Society of Medicine. 58(5): 295-300. PMC 1898525. This is similar to application of the factors set forth in the FDA Guidance, as discussed in my November 2018 Report.

²⁶ To the extent any of the additional evidence discussed herein was available as of 2008, it also supports the regulatory opinions provided in my November 2018 Report, as supplemented and clarified in this Supplement.

²⁷ See November 2018 Report at 39-47, as supplemented with additional evidence cited in this Supplement.

significant if derived from strong study design and methodology, which minimizes bias, the possibility of chance, and the role of confounders.²⁸

32. The strength of association factor is supported in this case by the following non-exhaustive list of key evidence.

32.1. I reviewed Sanofi's TAX 316 and TAX 301 clinical trial data including: (i) the rate of irreversible alopecia in the TAC arm at various points in time, as represented by Sanofi in internal documents and submissions to regulatory authorities and as described above in my discussion regarding the statistically significant increased risk of irreversible alopecia with Taxotere; and (ii) Dr. Madigan's statistical analysis of Sanofi's TAX 316 and TAX 301 clinical trial data from both annual submissions and the final clinical trial data, including his meta-analyses of this data, demonstrating a statistically significant increased risk of irreversible alopecia with the TAC arm versus the FAC comparator arm at multiple points in time including at the end of the clinical trials.²⁹

32.2. I also reviewed the publicly available medical literature and identified four comparative studies that contained sufficient data to perform a statistical analysis of irreversible alopecia reported with Taxotere-containing regimens as compared to regimens without Taxotere (Kang 2018, Martin 2018, Crown 2017, and Sedlacek 2006). A statistical analysis of the data presented in each of these studies, as confirmed by Dr. Madigan, demonstrates a statistically

²⁸ Lucas, Robyn M. et al. 2004. Association or causation: evaluating links between "environment and disease." Bulletin of W.H.O. 83(10).

²⁹ I have reviewed the transcripts from the testimony of Dr. Michael Kopreski played during the Barbara Earnest Taxotere trial regarding his re-analysis of the TAX 316 clinical trial. Dr. Kopreski's review is a post-hoc analysis of a small subset of limited interim data from one clinical trial that has not been independently verified, is not based on any clinical protocol plan, is not peer reviewed, is not final, locked data, and has never been submitted to any regulatory authority. In fact, from the date the final clinical trial data was locked in 2010, Sanofi presented data and statistical calculations both internally and in regulatory submissions that are consistent with the evidence I relied on in my November 2018 Report and this Supplement. *See, e.g.*, Sanofi's 2015 Causation Analysis; Taxotere 2018 Label; Taxotere 2019 Label; Sanofi_02540992; Sanofi_00811960; Sanofi_01101022; Sanofi_01331114.

significant increase of irreversible alopecia with Taxotere.³⁰ In addition, a pooled meta-analysis of these four comparative studies likewise demonstrates a statistically significant increased risk of irreversible alopecia.³¹

33. In addition, the strength of association factor is supported by paragraphs 127 through 133 of my November 2018 Report.

34. In my opinion, evidence exists to demonstrate that the strength of association between irreversible alopecia and Taxotere is statistically meaningful as compared to other chemotherapy agents.

ii. Consistency

35. The Bradford Hill consistency factor is similar to the FDA Guidance factor for frequency of reporting. I incorporate my discussion of this factor from my November 2018 Report herein.³²

36. The present application of this factor looks at the consistency of the outcome in a variety of different circumstances, such as among different populations or environments.³³

³⁰ The statistical analysis demonstrated that Crown (odds ratio 1.37, $p=0.80$), Sedlacek (odds ratio 54.7, $p=2.6 \times 10^{-5}$) and Martin (odds ratio 3.61, $p=1.2 \times 10^{-8}$) were all statistically significant. The fourth study, Kang, did not provide data regarding the number of patients receiving each regimen, but did provide an odds ratio comparing docetaxel to non-docetaxel treatment regimens of 8.01 (95% confidence interval 1.20-53.26).

³¹ a pooled analysis (random effects meta-analysis) of the adverse event rates for irreversible alopecia from the TAX 316 and TAX 301 clinical trials demonstrated that there is a statistically significant increased risk of irreversible alopecia for patients in the TAC arm versus the FAC arm (a rate ratio of 1.85 with a corresponding 95% confidence interval (1.04, 3.31) and a p-value of 0.04).

³² See November 2018 Report at 39-47, as supplemented with additional evidence cited in this Supplement.

³³ Lucas, Robyn M. et al. 2004. Association or causation: evaluating links between “environment and disease.” Bulletin of W.H.O. 83(10).

37. A useful tool to evaluate this factor is post-market surveillance, which is required of all drug manufacturers.³⁴ Post-market surveillance allows for the collection of real-world adverse event data across varying populations and environments.

38. The consistency factor is supported by the following non-exhaustive list of key evidence.

38.1. I reviewed Sanofi's internal global pharmacovigilance database for reports of irreversible alopecia.³⁵ In addition to the analysis of Sanofi's internal global pharmacovigilance database discussed in my November 2018 Report,³⁶ I also requested that Dr. Madigan calculate the number of reports (excluding reports labeled as "recovered") as a percentage of total alopecia reports.³⁷ Between 1999 and 2015, the range of reports of irreversible alopecia as a percentage of total alopecia reports ranged from 0.2% in 2001 to 52.3% in 2010, with an average of 18.04%.³⁸

38.2. I reviewed the medical literature for reports of irreversible alopecia with Taxotere-containing regimens, as detailed in my November 2018 Report and my updated Schedule 5, and identified reports of irreversible alopecia in as early as 2004 for Taxotere-

³⁴ See 21 CFR § 314.80(b).

³⁵ See Sanofi_04353203 (CIOMS Suspect Adverse Reaction Reports).

³⁶ See November 2018 Report ¶¶ 120-121.

³⁷ Madigan October 2019 Report at 20-21. This methodology is similar to the methodology used and reported by Sanofi in its 2015 Causation Analysis (reporting 5.3% reports of "permanent alopecia" out of the total alopecia reports in Sanofi's internal database), which I also reviewed. Sanofi_01268143. Although not specifically noted in the text of the document, Sanofi's 2011 Clinical Overview identified 8.8% of total alopecia reports in Sanofi's internal database as reporting "persistent alopecia." Sanofi_04353204.

³⁸ *Id.* The only years in which reports of irreversible alopecia as a percentage of total alopecia were below 1% occurred in 2001 and 2002. The lowest percentage in any other year between 1999 and 2015 was 4.3% in 2003. In 2008, 8.7% of total alopecia reports in Sanofi's internal database were reports of irreversible alopecia.

containing regimens used in the treatment of early stage breast cancer.³⁹ These reports have steadily increased over time.

38.3. I requested that Dr. Madigan perform an analysis of the FAERS database, which identified a safety signal between Taxotere and irreversible alopecia based on the application of several different disproportionality methodologies.⁴⁰

38.4. I reviewed internal Sanofi email correspondence and attachments from 2012 that detail the duration of follow-up for the 29 patients with ongoing alopecia at the end of the follow-up period in the TAX 316 clinical trial and all but one patient reported a follow-up duration of greater than 6 months.⁴¹

38.5. I reviewed internal Sanofi spreadsheets of call and web inquiries from physicians and patients reporting cases of irreversible alopecia and seeking information from Sanofi about the risk of irreversible alopecia with Taxotere.⁴² According to these spreadsheets, Sanofi began consistently receiving inquiries regarding irreversible alopecia in 2004.

39. In addition, the consistency factor is supported by paragraphs 110 through 126 of my November 2018 Report.

40. In my opinion, evidence exists to demonstrate the consistency of irreversible alopecia among patients treated with Taxotere.

³⁹ I have supplemented Schedule 5 to my November 2018 Report to provide a summary of the conclusions from the medical literature I identified, reviewed, and analyzed. An updated Schedule 5, Studies Regarding the Risk of Irreversible Alopecia Associated with Taxotere and Details of Other Studies Cited or Referenced in This Report, is attached to this Supplement. *See also* Sanofi_05969209.

⁴⁰ I have considered the methodology used to identify reports of irreversible alopecia with Taxotere in the FAERS database. As I previously stated at my deposition, safety signals from the FAERS database do not, in and of themselves, establish causation. While there are inherent limitations in FAERS analysis given the nature of the database, the proportionality analyses and search methodologies utilized to identify irreversible alopecia described herein are widely accepted tools for identifying safety signals.

⁴¹ Sanofi_05319538; *see also* Sanofi_05319537; Sanofi_02368847.

⁴² Sanofi_00792534 (List of inquiries regarding certain events of irreversible alopecia); Sanofi_00792535 (List of inquiries regarding certain events of irreversible alopecia).

iii. Biological Gradient

41. This Bradford Hill criteria is similar to the FDA Guidance factor for dose response. I incorporate my discussion of this factor from my November 2018 Report herein.⁴³

42. The biological gradient factor is supported by the following non-exhaustive list of key evidence.

42.1. I reviewed the publicly available medical literature and identified reports evidencing a dose-response relationship between Taxotere and irreversible alopecia, including Martin's 2018 study, Crown's 2017 study, and Bourgeois's 2014 presentation.⁴⁴

43. In addition, the biological gradient factor is supported by paragraphs 134 through 139 of my November 2018 Report.

44. In my opinion, evidence exists to demonstrate a biological gradient between irreversible alopecia and patients treated with Taxotere.

iv & v. Plausibility and Coherence

45. These two Bradford Hill criteria are similar to the FDA Guidance factor analyzing whether the adverse event is consistent with the pharmacology of the drug. I incorporate my discussion of this factor from my November 2018 Report herein.⁴⁵

46. As originally applied, biological plausibility had limited utility given the limitations in what is biologically knowable. The challenge of assessing biological plausibility remains, and the current interpretation of these factors evaluate whether the cause-and-effect

⁴³ See November 2018 Report at 47-48, as supplemented with additional evidence cited in this Supplement.

⁴⁴ See also Uptodate.com ("[T]here is now convincing evidence of permanent or prolonged alopecia after standard-dose chemotherapy for breast cancer (particularly with docetaxel, which is dose and duration dependent)").

⁴⁵ See November 2018 Report at 48-50, as supplemented with additional evidence cited in this Supplement.

interpretation of an association fits with what is presently known about the disease at issue.⁴⁶ In other words, is the adverse event consistent with the pharmacology of the drug.

47. The plausibility and coherence factors are supported by the following non-exhaustive list of key evidence.

47.1. Descriptions of biological plausibility in Sanofi's internal documents, including Sanofi's 2015 Causation Analysis.⁴⁷

47.2. I also reviewed the publicly available medical literature discussing the plausible biological mechanism of irreversible alopecia with Taxotere, including Fonia's 2017 study, Miteva's 2011 study, and Paus's 2013 study.

48. In addition, the plausibility and coherence factors are supported by paragraphs 140 through 149 of my November 2018 Report.

49. In my opinion, evidence exists to demonstrate that irreversible alopecia is biologically plausible and coheres to our current understanding of the pharmacology of Taxotere.

vi. Temporality

50. This Bradford Hill criteria is similar to the FDA Guidance factor for temporal association. I incorporate my discussion of this factor from my November 2018 Report herein.⁴⁸

51. The temporality factor is supported by the following non-exhaustive list of key evidence.

⁴⁶ Lucas, Robyn M. et al. 2004. Association or causation: evaluating links between "environment and disease." Bulletin of W.H.O. 83(10).

⁴⁷ See also Sanofi_05969184; Sanofi_05969189; Sanofi_05969209.

⁴⁸ See November 2018 Report at 50-51, as supplemented with additional evidence cited in this Supplement.

51.1. As indicated in the above discussions of the strength of association and consistency factors, and as discussed in my November 2018 report,⁴⁹ Sanofi received adverse event reports of irreversible alopecia occurring in patients following their exposure to Taxotere.

51.2. Likewise, I reviewed the medical literature for reports of irreversible alopecia with Taxotere-containing regimens, as detailed in my November 2018 Report and my updated Schedule 5, and identified reports of irreversible alopecia in patients following their exposure to Taxotere.

52. In addition, the temporality factor is supported by paragraphs 150 through 154 of my November 2018 Report.

53. In my opinion, evidence exists to demonstrate a temporal association between irreversible alopecia and Taxotere.

vii. Specificity

54. The Bradford Hill criteria for specificity is generally considered to be a weak or irrelevant factor from an epidemiologic standpoint. Rather, specificity is often evaluated by the occurrence of the adverse event and the rarity of occurrence of the event in the general population.

55. The specificity factor is supported by the following non-exhaustive list of key evidence.

55.1. I reviewed the publicly available medical literature review to identify reports of irreversible alopecia with other comparator regimens in the treatment of early-stage breast cancer, including reports prior to Taxotere's initial approval in 1996 and approval for

⁴⁹ See November 2018 Report ¶¶ 120-121.

early-stage breast cancer in 2004.⁵⁰ I could not locate any reports of irreversible alopecia for other comparator regimens in the treatment of early-stage breast cancer prior to the approval of Taxotere.⁵¹

55.2. I also reviewed the French Health Authorities response to Sanofi’s March 2011 Assessment of the Safety Review of Persistent Alopecia in Patients Treated with Docetaxel. According to the response, the French Health Authorities reviewed “[a]ll cases [of irreversible alopecia that] were reported since 1999 or 2000,” finding that “[b]efore this date, anthracyclines, anticancer drugs known to induce severe alopecia, were already used in the treatment of breast cancer, and no case of persistent alopecia was reported in published literature or in the French pharmacovigilance database.”⁵² This finding from the French Health Authorities is consistent with the results of my review of the publicly available medical literature of reports of irreversible alopecia as described above.

55.3. I requested that Dr. Madigan analyze the FAERS database for reports of irreversible alopecia with Taxotere and other comparator agents. Dr. Madigan found a safety signal between Taxotere and irreversible alopecia based on the application of several different disproportionality methodologies, but found no signal (or only a smaller, weakening signal) with

⁵⁰ See updated Schedule 5. I also reviewed the labels for other comparator or concomitant drugs, including Adriamycin, Cyclophosphamide, Taxol, and 5-Flourouracil, to analyze what information those labels provided about adverse reactions, including but not limited to the risk of temporary and irreversible hair loss, and to review when these drugs came on the market.

⁵¹ My Schedule 5 identifies some reports of irreversible alopecia with non-Taxotere regimens and also identifies that Taxotere is often administered in combination with other chemotherapy drugs. However, based upon my review and analysis, the number of reports of irreversible alopecia is greater and more consistently identified with Taxotere regimens than non-Taxotere regimens, and there are limited or no reports of irreversible alopecia with other chemotherapy drugs used in combination with Taxotere prior to Taxotere’s initial approval in 1996 or approval for early stage breast cancer in 2004.

⁵² Sanofi_02540992.

all other comparator drugs.⁵³ In addition, a lasso logistic regression analysis of the FAERS data demonstrated an approximately 10-fold increased reporting rate of Taxotere and irreversible alopecia against all other drugs. The logistic regression analysis demonstrated that the risk of irreversible alopecia with docetaxel became statistically significant with Taxotere compared to all other drugs in 2003 and continued through the end of his analysis in 2017.

56. In my opinion, evidence exists to demonstrate the specificity factor between irreversible alopecia and Taxotere.

viii. Analogy

57. The Bradford Hill criteria for analogy is similar to the FDA Guidance factor analyzing whether the adverse event is known to be caused by related drugs. I incorporate my discussion of this factor from my November 2018 Report herein.⁵⁴

58. In evaluating this factor, I reviewed the medical publicly available medical literature, Sanofi's clinical trial data, and Dr. Madigan's analysis of the FAERS data. Based on my review, while many of these drugs are associated with alopecia, reports regarding irreversible alopecia are more prevalent and consistent with Taxotere than these other drugs.⁵⁵

⁵³ The data in FAERS dates back to 1969. As of 1996 when Taxotere was initially approved, there were zero reports of irreversible alopecia in FAERS for any of the comparator drugs. As of 2004 when Taxotere was approved for early stage breast cancer, there were still zero reports of irreversible alopecia in FAERS for doxorubicin and cyclophosphamide.

⁵⁴ See November 2018 Report at 52-54, as supplemented with additional evidence cited in this Supplement.

⁵⁵ As noted above, my updated Schedule 5 identifies some reports of irreversible alopecia with non-Taxotere regimens and also identifies that Taxotere is often administered in combination with other chemotherapy drugs. However, based upon my review and analysis, the number of reports of irreversible alopecia is greater and more consistently identified with Taxotere regimens than non-Taxotere regimens, and there are limited or no reports of irreversible alopecia with other chemotherapy drugs used in combination with Taxotere prior to Taxotere's initial approval in 1996 or approval for early stage breast cancer in 2004. Also, the data in FAERS dates back to 1969. As of 1996 when Taxotere was initially approved, there were zero reports of irreversible alopecia in FAERS for any of the comparator drugs. As of 2004 when Taxotere was approved for early stage breast cancer, there were still zero reports of irreversible alopecia in FAERS for doxorubicin and cyclophosphamide.

59. Based on my discussion of the factors above, my opinion is that there is insufficient evidence to conclude that other related drugs are also known to cause irreversible alopecia.

ix. Experiment

60. The Bradford Hill factor for experiment is similar to the FDA Guidance factor for dechallenge and rechallenge. I incorporate my discussion of this factor from my November 2018 Report herein,⁵⁶ and as stated there is insufficient information to assess this Bradford Hill factor due to ethical considerations.⁵⁷

x. Summary of Bradford Hill Criteria

61. In my opinion, based on my application of the Bradford Hill criteria, a substantial number of the Bradford Hill criteria are satisfied.

C. Summary of General Causation Opinion

62. Based on my review and analysis of the available scientific evidence, including the evidence of a statistically significant increased risk of irreversible alopecia with Taxotere, and my application of the Bradford Hill factors finding that a substantial number of the Bradford Hill criteria are satisfied, it is my opinion to a reasonable degree of medical probability that there is more likely than not a causal relationship between Taxotere and irreversible alopecia.

63. My opinion that there is a causal relationship between Taxotere and irreversible alopecia is supported by statements from Sanofi's employees.

63.1. Amy Freedman, M.D., Sanofi's Global Safety Officer, testified:

⁵⁶ See November 2018 Report at 52-54, as supplemented with additional evidence cited in this Supplement.

⁵⁷ See November 2018 Report at 51-52 regarding my prior discussion of the FDA Guidance re-challenge, de-challenge factor.

Q. Based upon your knowledge at Sanofi in 2006, Sanofi knew that Taxotere could cause irreversible alopecia, correct?

A. Yes.⁵⁸

63.2. Leslie Fierro, Sanofi's Head of Medical Information Services, testified:

Q. Let me ask you this: as a pharmacist, do you understand today that Taxotere can cause permanent hair loss?

A. Correct, yes.⁵⁹

63.3. Nanae Hangai, M.D., Ph.D., Sanofi's Global Safety Officer, testified that "Docetaxel/Taxotere may cause permanent hair loss, but it's case-by-case."⁶⁰

63.4. In January 2007, in an informed consent form drafted by Sanofi for a Phase II clinical trial at the Cross Cancer Institute in Canada, Sanofi represented that "hair loss" was a Reported Side Effect of Adriamycin and Cyclophosphamide, but "permanent hair loss" was a Reported Side Effect of Docetaxel.⁶¹

64. In addition, my opinion that there is a causal relationship between Taxotere and irreversible alopecia is supported by subscription based resources, such as UpToDate, which are designed to provide clinical information to physicians. For instance, the information contained in UpToDate⁶² regarding permanent chemotherapy induced alopecia states: "[s]ome

⁵⁸ Deposition of Amy Freedman, M.D., dated October 26, 2018, at 195:20-196:2.

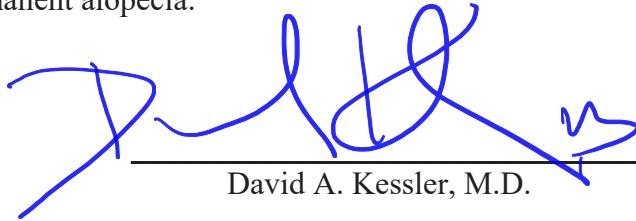
⁵⁹ Deposition of Leslie Fierro, dated January 17, 2019, at 89:22-90:1.

⁶⁰ Deposition of Nanae Hangai, M.D., PhD, dated February 1, 2018, at 17:23-18:2.

⁶¹ Sanofi_01034325, Sanofi_03029992 (Palatinsky Ex. 19). *Compare with* Ochsner Clinic Foundation Research Informed Consent, December 12, 2006.

⁶² Information in UpToDate is authored by a subject matter expert and reviewed by at least two separate physician reviewers. "This group works together to perform a comprehensive review of the literature, culminating in clear recommendations for treatment and screening which allow clinicians to improve care. These recommendations are always based on evidence." UpToDate Editorial Process, <https://www.uptodate.com/ja/node/261>.

chemotherapy agents may cause prolonged or permanent alopecia, including docetaxel given at doses of 75 mg/m² or higher per cycle, although the true incidence is unknown (see 'Recovery and reversibility' below). It is important to advise patients about this risk before starting treatment with a specific regimen, as treatment alternatives may be available if patients are bothered by the possibility of permanent alopecia.”⁶³



David A. Kessler, M.D.

10/ 21/ 2019

Date

⁶³ *Id.* (also stating that “there is now convincing evidence of permanent or prolonged alopecia after standard-dose chemotherapy for breast cancer (particularly with docetaxel, which is dose and duration dependent) The impact of hair loss and potential alternative chemotherapy approaches should be discussed with each patient **before** the initiation of therapy that may lead to alopecia. This preemptive approach is important for minimizing the emotional distress associated with hair loss. For patients with breast cancer who are receiving docetaxel at doses higher than 75 mg/m² per infusion, it is important to advise patients about the risk of prolonged or permanent alopecia.”).

EXHIBIT J

Filed Under Seal

EXHIBIT J

EXPERT REPORT
DAVID A. KESSLER, M.D.

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¹ All schedules were prepared by legal staff at my request and subject to my review.

I. QUALIFICATIONS

1. My name is David A. Kessler, M.D. I received my M.D. degree from Harvard Medical School in 1979 and my J.D. degree from the University of Chicago Law School in 1978.

2. I did my pediatrics training at Johns Hopkins Hospital.

3. I was appointed in 1990 by President George H. W. Bush as Commissioner of the United States Food and Drug Administration (“FDA”) and was confirmed by the United States Senate. I also served in that position under President William Jefferson Clinton until February 1997.

4. I have taught food and drug law at Columbia University Law School, and I have testified many times before the United States Congress on food, drug, and consumer protection issues under federal and state law. Over the last thirty years, I have published numerous articles in legal, medical, and scientific journals on the federal regulation of food, drugs, and medical devices. I have had special training in pharmacoepidemiology at Johns Hopkins Hospital. My resume, including a list of my published books and articles, is included in Appendix A. A list of cases in which I have appeared as a witness in the last five years, and documentation of my expert witness fee, is attached as Appendix B.

5. As Commissioner, I had ultimate responsibility for implementing and enforcing the United States Food, Drug, and Cosmetic Act. I was responsible for overseeing five Centers within the FDA. They included, among others, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health and the Center for Biologics Evaluation and Research. In addition to those duties, I placed high priority on getting promising therapies for serious and life-threatening diseases to patients as quickly as possible. During my tenure as Commissioner, the FDA announced a number of new programs including: the regulation of the marketing and sale of tobacco products to children; nutrition labeling for food; user fees for

drugs and biologics; preventive controls to improve food safety; measures to strengthen the nation's blood supply; and the MEDWatch program for reporting adverse events and product problems involving both drugs and devices. I created an Office of Criminal Investigation within the Agency to investigate suspected criminal violations of the Food, Drug, and Cosmetic Act, FDA regulations, and other related laws. I worked closely with and was ultimately responsible for the FDA's Division of Drug Marketing, Advertising and Communications. I have published articles on drug promotion and marketing practices.²

6. I am a senior advisor to TPG Capital, a leading global private equity firm, which owns pharmaceutical and biomedical companies. I previously served on the board of Aptalis Pharma and Tokai Pharmaceuticals, and I currently serve on the board of the medical device and biologics company Immucor, Inc. In these advisory and fiduciary capacities, I have advised companies on the standards and duties of care within the pharmaceutical and medical device industry. I also previously chaired the compliance committees of both Aptalis, and I currently chair the quality committee of Immucor, which involves ensuring compliance with FDA laws and requirements.

7. The documents provided to me by counsel, or that I accessed independently from various sources, including but not limited to the FDA's website, are listed in Appendix C to this report. Based on my review of those documents and my training and experience, I have a number of opinions that are detailed below.

² These include: "The federal regulation of prescription drug advertising and promotion." (*JAMA*. 1990 Nov 14;264(18):2409-15); "Drug promotion and scientific exchange. The role of the clinical investigator." (*N Engl J Med*. 1991 Jul 18;325(3):201-3); "Communicating with patients about their medications." (*N Engl J Med*. 1991 Dec 5;325(23):1650-2); "Therapeutic-class wars--drug promotion in a competitive marketplace." (*N Engl J Med*. 1994 Nov 17;331(20):1350-3); and "Direct-to-consumer advertising: is it too late to manage the risks?" (*Ann Fam Med*. 2007 Jan-Feb;5(1):4-5).

II. SCOPE OF EXPERT OPINIONS

8. It is my understanding that the cases in this litigation include but are not limited to the following claims as they relate to docetaxel/Taxotere (hereinafter referred to as “Taxotere”): failure to warn and misrepresentation claims based on strict products liability and negligence theories, fraudulent misrepresentation, fraudulent concealment, and fraud and deceit.

9. In this report, I use the term “Sanofi” to refer to Sanofi US Services Inc. f/k/a Sanofi Aventis U.S. Inc. Sanofi-Aventis U.S. LLC, and their affiliates, subsidiaries, successors, and assigns.

10. My understanding is that the bellwether plaintiffs at this time include, but are not limited to: 1) Antoinette Durden v. Sanofi S.A., et al., Case No. 2:16-cv-166335; 2) Tanya Francis v. Sanofi S.A., et al., Case No. 2:16-cv-17410; and 3) Barbara Earnest v. Sanofi S.A., et al., Case No. 2:16-cv-17144.³

11. I have been asked to address Sanofi’s duty to warn physicians and patients about the risks of irreversible⁴ hair loss associated with Taxotere from the years 1990 to 2015 and, because of the date of Taxotere administration to the bellwether plaintiffs cited above, to specifically provide opinions about Sanofi’s duty by as early as 2009.⁵

III. DEVELOPMENT OF TAXANES AND REGULATORY OVERVIEW OF TAXOTERE

12. Taxanes are a class of drugs that includes Taxotere.

³ See Schedule 2, MDL Bellwether Cases.

⁴ I use the term “irreversible” in this Report to distinguish between the temporary and non-temporary nature of this injury. For purposes of this Report, however, “irreversible” also includes other non-temporary descriptions, including but not limited to: chronic, permanent, long-term, ongoing, persistent, and persisting. The definition of “irreversible” hair loss is more fully discussed below in Section V of this Report.

⁵ I reserve the right to study the issues at both earlier and later dates. I also reserve the right to supplement this report should additional documents or information be produced.

13. In 1962, the U.S. Department of Agriculture, under contract to the National Cancer Institute (“NCI”) collected bark from the Pacific yew tree, *Taxus brevifolia*, as part of their natural products screening program.⁶ Under this program, the NCI looked to find natural products that might cure cancer.⁷

14. By 1966, researchers discovered that extracts from the bark of the Pacific yew tree had cytotoxic activity against cultures of carcinoma cells.⁸ The active component was isolated and called paclitaxel.⁹ Due to the scarcity of the compound—a half a gram of taxol required twelve kilograms of dried bark and a Pacific yew tree yielded approximately two kilograms—researchers looked to synthesize the compound.¹⁰

15. In 1984, NCI began phase I clinical trials of paclitaxel extracted from bark of the Pacific yew tree.¹¹ Following initial encouraging results, NCI convened workshops in 1990 and 1992 to discuss the importance of the paclitaxel and strategize solutions to the drug’s supply problem.

16. In addition, to address the supply issue, NCI sought collaboration with private industry, and in 1991, NCI signed a Cooperative Research and Development Agreement with Bristol-Myers Squibb (“BMS”).¹² BMS received the marketing rights for paclitaxel and access to

⁶ Donehower R. (1996). The Clinical Development of Paclitaxel: A Successful Collaboration of Academia, Industry, and the National Cancer Institute. *The Oncologist* 1:240.

⁷ (Sanofi_02489593 at 3); Donehower R. (1996). The Clinical Development of Paclitaxel: A Successful Collaboration of Academia, Industry, and the National Cancer Institute. *The Oncologist* 1:240.

⁸ Donehower R. (1996). The Clinical Development of Paclitaxel: A Successful Collaboration of Academia, Industry, and the National Cancer Institute. *The Oncologist* 1:240.

⁹ (Sanofi_02489593 at 3).

¹⁰ *Discovery of Camptothecin and Taxol*, National Historic Chemical Landmark – American Chemical Society. April 23, 2003.

¹¹ Donehower R. (1996). The Clinical Development of Paclitaxel: A Successful Collaboration of Academia, Industry, and the National Cancer Institute. *The Oncologist* 1:240.

¹² Stephenson F. (2002). Tale of Taxol, <http://www.whale.to/cancer/taxol5.html>.

the data from ongoing and completed clinical trials.¹³ They also assumed responsibility for supplying paclitaxel for clinical trials as well as rapid development of a new drug application.¹⁴ In 1992, under my direction as Commissioner,¹⁵ the FDA approved Taxol for the treatment “of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy.”¹⁶

17. Following the publication of paclitaxel’s mechanism of action during initial drug development,¹⁷ researchers at Le Centre National de la Recherche Scientifique (CRNS) analysed specimens from a different yew tree, *Taxus baccata*, known as the common yew tree.¹⁸ In the needles of the common yew, the researchers discovered docetaxel, a compound having cytotoxic activity similar to taxol.¹⁹ In 1981, the researchers began working to synthesize this compound under a collaboration agreement with Rhône-Poulenc Rorer S.A., the predecessor company to Sanofi.²⁰

18. In 1986, chemists at Rhône-Poulenc patented docetaxel,²¹ and the results of early in vivo studies showed that 56 976 R.P. had greater antitumor than paclitaxel.²²

19. Sanofi began Taxotere phase I clinical trials in 1990.²³ The first results, published

¹³ *Id.*

¹⁴ *Id.*

¹⁵ See https://www.washingtonpost.com/archive/politics/1992/12/30/fda-approves-taxol-to-treat-cancer/efc4e378-b90d-4de0-baa8-e1d4678ac6e0/?utm_term=.6bb2491ffa25.

¹⁶ FDA Approval Letter to Bristol-Myers Squibb Co.

¹⁷ Horowitz S. (1979). Promotion of Microtubule Assembly In Vitro by Taxol. *Nature* 277:665.

¹⁸ Muriel Le Roux and Francoise Gueritte, *Navelbine and Taxotere*, 174 (2017).

¹⁹ *Id.*

²⁰ (Sanofi_02489593 at 4); Muriel Le Roux and Francoise Gueritte, *Navelbine and Taxotere*, 177 (2017).

²¹ (Sanofi_02489593 at 5); Muriel Le Roux and Francoise Gueritte, *Navelbine and Taxotere*, 206 (2017).

²² Muriel Le Roux and Francoise Gueritte, *Navelbine and Taxotere*, 203 (2017).

²³ (Sanofi_02489593 at 8); Muriel Le Roux and Francoise Gueritte, *Navelbine and Taxotere*, 216 (2017).

the next year, indicated clinical activity against breast and ovarian cancers.²⁴ The promising phase I results prompted Sanofi to start phase II clinical trials in May 1992.²⁵

20. On July 27, 1994, Sanofi applied for FDA approval for Taxotere under NDA 20449 based on the results of the phase I and II clinical trials for the following indications: (1) “metastatic breast cancer patients in whom previous chemotherapy failed” and (2) “locally advanced or metastatic non-small cell lung cancer patients after failure of platinum based chemotherapy.”²⁶ In December 1994, the FDA’s Oncologic Drugs Advisory Committee unanimously decided to withhold approval of the drug, requesting more data on toxicity and additional phase III trials.²⁷

21. Taxotere was first approved by the European Union on April 12, 1995 for the treatment of locally advanced or metastatic breast cancer.²⁸

22. On October 17, 1995 the FDA’s Oncologic Drugs Advisory Committee (“ODAC”) voted 6 to 1 in favour of approving Taxotere for the treatment of metastatic breast cancer patients who were anthracycline-resistant.²⁹

23. On May 14, 1996, while I was Commissioner, the FDA approved Taxotere for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.³⁰

24. On December 23, 1999, the FDA approved Taxotere for treatment of patients with

²⁴ Muriel Le Roux and Francoise Gueritte, *Navelbine and Taxotere*, 217 (2017).

²⁵ (Sanofi_02489593 at 9); Muriel Le Roux and Francoise Gueritte, *Navelbine and Taxotere*, 217 (2017).

²⁶ (Sanofi_02489593 at 22).

²⁷ (Sanofi_02489593 at 23); *FDA Withholds Approval for Taxotere*, 6 ANNALS OF ONCOLOGY 200 (1995).

²⁸ (Sanofi_02489593 at 27).

²⁹ (Sanofi_02489593 at 28).

³⁰ (Sanofi_02489593 at 29). As a condition of approval, Sanofi made a post-marketing commitment to complete four controlled clinical trials and submitting completed findings of these studies for FDA review. FDA Approval Letter to Rhone-Poulenc Rorer dated May 14, 1996.

locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.³¹

25. On November 27, 2002, the FDA approved Taxotere for use in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.³²

26. On May 19, 2004, the FDA approved Taxotere for use in combination with prednisone as a treatment for patients with androgen independent (hormone refractory) metastatic prostate cancer.³³

27. On August 18, 2004, the FDA approved Taxotere in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.³⁴

28. On March 22, 2006, the FDA approved Taxotere in combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.³⁵

29. On October 17, 2006, the FDA approved Taxotere in combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable locally advanced

³¹ (Sanofi_02489593 at 35).

³² (Sanofi_02489593 at 87); FDA Approval Letter to Aventis Pharmaceuticals, dated November 27, 2002.

³³ (Sanofi_02489593 at 47).

³⁴ (Sanofi_02489593 at 57). As explained above, Sanofi submitted interim clinical trial data to support approval of this indication. As a condition to approval, Sanofi made a post-marketing study commitment to provide a complete report of this data. *See* FDA Approval Letter to Aventis Pharmaceuticals, August 18, 2004 (“To submit a complete report of the updated TAX316 data to verify the efficacy based on 700 events of DFS and safety of Taxotere in the adjuvant treatment of women with operable node- positive breast cancer and to submit the final analysis of overall survival (expected to occur in the year 2010).”).

³⁵ (Sanofi_02489593 at 69). FDA Approval Letter to Sanofi-Aventis U.S., Inc., dated March 22, 2006.

squamous cell carcinoma of the head and neck (SCCHN).”³⁶ On September 28, 2007, the FDA approved the use of Taxotere in combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).³⁷

30. On May 13, 2010, the FDA approved a change in the label to add language related to pediatric safety and efficacy.³⁸

31. After responding to a March 2015 FDA request for “a summary of cases of permanent partial or total alopecia associated with docetaxel use,”³⁹ Sanofi submitted a CBE sNDA on November 24, 2015 concerning “permanent or irreversible alopecia.”⁴⁰ In November-December 2015, FDA and Sanofi agreed to add the statement “Cases of permanent alopecia have been reported,”⁴¹ which Sanofi implemented “In accordance with 21 CFR 314.70(c) [Changes Being Effected].”⁴² On December 11, 2015, the FDA approved the CBE sNDA.⁴³

32. Sanofi submitted a sNDA on April 11, 2018 under section 505(b) of the FDCA concerning the risk of adverse events during the TAX 316 clinical trial study and adverse events

³⁶ (Sanofi_02489593 at 87); FDA Approval Letter to Sanofi-Aventis U.S., Inc., dated October 17, 2006.

³⁷ (Sanofi_02489593 at 87); FDA Approval Letter to Sanofi-Aventis U.S., Inc., dated September 28, 2007.

³⁸ (Sanofi_02489593 at 83). Prior to this time, in 2009, Sanofi submitted a sNDA to FDA seeking approval for a node-negative adjuvant breast cancer indication. However, after receiving “clear FDA feedback from FDA on the risk of filing this application,” Sanofi withdrew its application. E-mail from Linda Gustavson dated July 15, 2009 (Sanofi_01031668) (“This decision is based on the short duration of patent remaining, the risk of filing, the limited market interest in the U.S. and the desire to maintain credibility with FDA based on our successful approvals of Taxotere over the years.”); *see also* FDA Responses to Sponsor’s Questions (Sanofi_01246597) (“We are concerned about the small improvement in DFS in the face of the increased risk of toxicity in the TAC regimen. It is not clear that the benefit risk ratio is favorable.”).

³⁹ Email from Frank Cross, Jr. to Frances Polizzano, Mar. 23, 2015 (Sanofi_04878450).

⁴⁰ FDA Approval Letter to Sanofi-Aventis U.S. LLC dated December 11, 2015.

⁴¹ FDA PAS for alopecia, Review completed Dec. 4, 2015 for NDA #020449.

⁴² Letter from Frances Polizzano to FDA’s Geoffrey Kim, Nov. 24, 2015 (Hangai Ex. 18; (Sanofi_03333249).

⁴³ *Id.*

that persisted following completion of the study, including but not limited to alopecia.⁴⁴ On October 5, 2018, the FDA approved the sNDA.⁴⁵

IV. THE ROLE OF THE DRUG MANUFACTURER AND THE FDA

A. The Purveyor Of A Drug Has Primary Responsibility For A Drug's Safety

33. It is the purveyor of a drug that is responsible for the safety of its product.

34. A drug company has a responsibility, independent of what the FDA directs it to do, to alert physicians and patients to risks that were unknown to or poorly understood by the FDA, but were known to the company.⁴⁶ This duty predates by decades the advent of federal regulation of drugs. *See, e.g., Thomas v. Winchester*, 6 N.Y. 397 (1852).

35. FDA regulation of a drug cannot anticipate and protect against all safety risks to individual consumers. Even the most thorough regulation of a product may fail to identify potential problems presented by the product.

36. As I have written and testified about before the United States Congress, the Food, Drug, and Cosmetic Act grants the FDA substantial authority over the approval, labeling, and promotion of pharmaceutical products. But, in my opinion, nothing in the Food, Drug, and Cosmetic Act, or in the FDA's implementing regulations, relieves a manufacturer of its duty to act according to the company's knowledge about a product and its potential risks.

37. It was my opinion while Commissioner of the FDA, and remains to this day, that the two systems of state consumer protection (including potential product liability) and federal food and drug regulation should and do operate in a complementary but independent manner.

⁴⁴ FDA Approval Letter to Sanofi-Aventis U.S. LLC dated October 5, 2018, at https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2018/020449Orig1s079ltr.pdf.

⁴⁵ *Id.* *See also* Schedule 3, Taxotere Indications; Schedule 4, Alternative Therapies for the Types of Cancer for Which Taxotere is Indicated.

⁴⁶ *See* Schedule 1, Prior and Current FDA Regulations Regarding Manufacturers' Duties and Responsibilities.

38. As the Supreme Court has recently ruled, generally, state law imposes responsibilities on pharmaceutical companies to create products that are “reasonably safe,” a duty that can be satisfied by the “presence and efficacy of a warning to avoid an unreasonable risk of harm from hidden dangers or from foreseeable uses.”⁴⁷

39. The Institute of Medicine and Government Accountability Office has noted that the FDA’s ability to oversee drug safety has been constrained, especially during the post-approval portions of a drug’s life. Specifically, the Institute of Medicine, in its report titled, “The Future of Drug Safety: Promoting and Protecting the Health of the Public,” stated: “the drug safety system is impaired by the following factors: serious resource constraints that weaken the quality and quantity of the science that is brought to bear on drug safety; an organizational culture in CDER [Center for Drug Evaluation and Research] that is not optimally functional; and unclear and insufficient regulatory authorities particularly with respect to enforcement.” The report further stated: “the committee found that the FDA, contrary to its public health mission, and the pharmaceutical industry, contrary to its responsibility to the users of its products (and its shareholders), do not consistently demonstrate accountability and transparency to the public by communicating safety concerns in a timely and effective fashion.”⁴⁸

40. In its report titled “Drug Safety: Improvement Needed in FDA’s Postmarket Decision-Making and Oversight Process,” the General Accounting Office stated:

Two organizationally distinct FDA offices, the Office of New Drugs (OND) and the Office of Drug Safety (ODS), are involved in postmarket drug safety

⁴⁷ *Mut. Pharm. Co. Inc. v. Bartlett*, 133 S.Ct. 2466, 2480 (2013) (internal citations omitted); *see also Hill v. Searle Labs*, 884 F.2d 1064, 1068 (8th Cir. 1989) (“FDA regulations are generally minimal standards of conduct . . .”); *Wells v. Ortho Pharm. Corp.*, 788 F.2d 741, 746 (11th Cir. 1986) (“An FDA determination that a warning is not necessary may be sufficient for federal regulatory purposes but still not be sufficient for state tort law purposes.”); *Feldman v. Lederle Lab.*, 125 N.J. 117, 121 (N.J. 1991); *Vautour v. Body Masters Sports Indus.*, 147 N.H. 150, 153-54 (2001).

⁴⁸ Institute of Medicine, “The Future of Drug Safety: Promoting and Protecting the Health of the Public,” 2007, p.4; http://www.nap.edu/openbook.php?record_id=11750&page=4.

activities. OND, which holds responsibility for approving drugs, is involved in safety activities throughout the life cycle of a drug, and it has the decision-making responsibility to take regulatory actions concerning the postmarket safety of drugs. OND works closely with ODS to help it make postmarket decisions. ODS, with a primary focus on postmarket safety, serves primarily as a consultant to OND and does not have independent decision-making responsibility. ODS has been reorganized several times over the years. There has been high turnover of ODS directors in the past 10 years, with eight different directors of the office and its predecessors. In the four drug case studies GAO examined, GAO observed that the postmarket safety decision-making process was complex and iterative . . . FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues. The process has been limited by a lack of clarity about how decisions are made and about organizational roles, insufficient oversight by management, and data constraints. GAO observed that there is a lack of criteria for determining what safety actions to take and when to take them. Certain parts of ODS's role in the process are unclear, including ODS's participation in FDA's scientific advisory committee meetings organized by OND. Insufficient communication between ODS and OND has been an ongoing concern and has hindered the decision-making process. ODS does not track information about ongoing postmarket safety issues, including the recommendations that ODS staff make for safety actions. FDA faces data constraints in making postmarket safety decisions. There are weaknesses in the different types of data available to FDA, and FDA lacks authority to require certain studies and has resource limitations for obtaining data.⁴⁹

41. Risks that are rare, appear as common illnesses, have long latency periods, result from drug interactions, or have adverse impacts on subpopulations may go undetected in clinical testing. However, if a drug company has reason to know that the risks of a drug may result in adverse events, it has a responsibility to investigate them and to inform physicians and health care providers.

42. Generally, the FDA does not test the safety or effectiveness of drugs nor conduct clinical trials. That is the responsibility of the manufacturer. The FDA can approve a company's drug application or take steps to withdraw a drug that is on the market. In certain instances,

⁴⁹ Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process, GAO-06-402, March 31, 2006, Introduction page, <http://www.gao.gov/new.items/d06402.pdf>.

individuals at the FDA have undertaken research analyses on specific questions.⁵⁰ Such research analyses do not take the place, nor relieve the manufacturer, of its responsibility to assure the safety and effectiveness of its drug. Prior to 2007, once a drug was on the market, the FDA had limited authority to require a company to conduct clinical trials or to change the drug's label. In these instances, the FDA was left to "negotiate" with the drug company.⁵¹

43. As Dr. Sandra L. Kweder, Deputy Director of the Office of New Drugs for the FDA, testified on March 1, 2005, before the U.S. Congress Committee on Health, Education, Labor, and Pensions:

"Q. On the clinical trial, the FDA cannot order a company to do a clinical trial, is that correct?"

A. That is correct."⁵²

44. Once a drug is approved, the FDA's regulations make clear that a drug company has a duty to warn and modify labeling without delay when hazards emerge with one of its drugs.⁵³ The regulations specifically authorize a drug company to make labeling changes, and

⁵⁰ See, e.g., Rosa F. (1991). Spina Bifida in Infants of Women Treated with Carbamazepine During Pregnancy. *New England J. Med.* 324 (Vol. 10): 674-77.

⁵¹ The FDCA was amended in 2007. "For the first time, it granted the FDA statutory authority to require a manufacturer to change its drug label based on safety information that becomes available after a drug's initial approval." *Wyeth v. Levine*, 555 U.S. 555, 567 (2009). "The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge. State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information. Failure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." *Id.* at 578-579. Also, authority was granted allowing the FDA to require further studies and clinical trials. As summarized by the FDA: "Section 505(o)(3) of the Act authorizes FDA to require postmarketing studies or clinical trials at the time of approval or after approval if FDA becomes aware of new safety information In some cases, FDA may be concerned about a risk and believe that it is serious, but may not know enough about the risk to determine how to address the risk in labeling and what information would be appropriate to include. In such a case, FDA can require a postmarketing study or clinical trial to obtain more information." USDHHS, FDA, *Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*, at 3-4 (April 2011). The 2007 amendment complements, but does not replace, the manufacturer's primary duty to provide adequate warnings of safety hazards associated with its products.

⁵² Hearing, March 1, 2005, FDA's Drug Approval Process: Up to the Challenge?, S.Hrg. 109-67, at 24.

⁵³ 21 CFR 201.57(e) (1999).

take other steps to inform physicians and patients of emerging risks, without advanced approval from the FDA.⁵⁴ Such responsibility is intended to complement, not undercut, the FDA's job of protecting consumers from dangerous drugs.

45. The FDA has stated that nothing in FDA's regulations prohibit a manufacturer from warning doctors and patients whenever possible. As the FDA stated in 1979: "The Commissioner also advises that these labeling regulations do not prohibit a manufacturer, packer, relabeler, or distributor from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered. The addition to labeling and advertising of additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drug, or the issuance of letters directed to health care professionals (e.g., 'Dear Doctor' letters containing such information) is not prohibited by these regulations."⁵⁵

46. Manufacturers have superior resources that are or should be committed to overseeing the safety of the drugs they market. As a result, manufacturers invariably get safety information before the FDA does and have access to information that is not available to the FDA. Company scientists and physicians also develop impressions and understanding of a drug's potential safety profile that may be more informed than the FDA's.

47. Thus, what a drug company knows about a drug and what the FDA knows may be different.

48. The duties of a pharmaceutical company are based not only on FDA laws and regulations, but also on the risks presented by a drug about which the company knew, should have known, or should have investigated.

⁵⁴ For a discussion of the procedure for making changes to a black box, *see* Section IV(E) in this report below.

⁵⁵ 44 F.R. 37434 at 37447 (June 26, 1979).

49. In my opinion, Sanofi's responsibility for the safety of its product and the adequacy of its warnings exists regardless of what the FDA did or did not do.

50. As Commissioner of the FDA from 1990 through 1997, I can attest that the responsibility of drug sponsors has been in force for decades.

51. In my opinion, in light of the FDA's limited resources and scope, the purveyor of a drug, not the FDA, has primary responsibility for the safety of its product.

52. The manufacturer has the responsibility to ensure the safety of its drug both prior to marketing and after the drug has been approved and is on the market.

53. The manufacturer has the responsibility to understand a drug's safety risks both pre- and post-marketing.

54. In essence, the manufacturer must constantly study and convey the risks associated with the drug throughout a drug's life history.

55. The manufacturer must update the drug's label with new safety information throughout a drug's life history.

56. To ensure the safety of its drug, a manufacturer must analyze a drug's safety profile throughout a drug's life history.

57. As the FDA has stated: "Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization."⁵⁶

⁵⁶ FDA, Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf>.

B. A Drug Manufacturer's Responsibility To Investigate And Disclose Risks After A Drug Is On The Market

58. The drug manufacturers' responsibility to assure the safety of their drugs throughout the life of the drug is to assure the safety and efficacy of a drug prior to approval and also after the drug is on the market.

59. Under United States food and drug laws, a drug may not be introduced into interstate commerce unless its sponsor has shown that the drug is safe and effective for the intended conditions of use.⁵⁷

60. The law requires that "adequate and well-controlled investigations" be used to demonstrate a drug's safety and effectiveness.⁵⁸

61. The FDA approves a drug if there are "adequate and well-controlled" clinical trials that demonstrate a drug's safety and effectiveness for its intended conditions of use.⁵⁹

62. The "intended conditions" for use of a drug are listed in the drug's labeling which is reviewed and approved by the FDA.⁶⁰

63. Indications for use that are not listed in a drug's labeling have not been approved by the FDA.⁶¹

⁵⁷ 21 U.S.C. § 355.

⁵⁸ 21 U.S.C. § 355(d)(7).

⁵⁹ 21 U.S.C. § 355(d)(7).

⁶⁰ 21 U.S.C. §§ 355(d)(1) and (2).

⁶¹ "The labeling is derived from the data submitted with the new drug application. It presents a full disclosure summarization of drug use information, which the supplier of the drug is required to develop from accumulated clinical experience and systemic drug trials of preclinical investigations and adequate, well-controlled clinical investigations that demonstrate the drug's safety and the effectiveness it purports or is represented to possess." (37 Fed. Reg. 16,503 (1972)).

64. The following standards are based on my experience as FDA Commissioner from 1990 to 1997, having written about and taught food and drug law, dealt with FDA statutes and regulations and acted as chair of compliance committees of FDA-regulated companies.

65. In 1979, FDA, as part of a final rule titled “Labeling and Prescription Drug Advertising: Content and Format for Labeling for Human Prescription Drugs⁶²” issued 21 CFR §§ 201.57 (e) and (g) which stated, respectively:⁶³

“(e) Warnings: Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.”⁶⁴

“(g) Adverse Reactions: An adverse reaction is an undesirable effect reasonably associated with the use of the drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.”⁶⁵

66. In 2006, FDA adopted final rules for 21 CFR §§ 201.57 (c)(6) and (7) which stated:

“(c)(6) 5 Warnings and precautions. (i) General. This section must describe clinically significant adverse reactions....the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established....” “(c)(7) 6 Adverse reactions. This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.”⁶⁶

⁶² 44 Fed. Reg. 37434 (June 26, 1979).

⁶³ 44 Fed. Reg. 37434 (June 26, 1979) at 37465.

⁶⁴ 21 CFR § 201.57(e) (emphasis added).

⁶⁵ 21 CFR § 201.57(g) (emphasis added).

⁶⁶ 71 Fed. Reg. 3922-3997 (January 24, 2006) at 3990.

67. Also under 21 C.F.R. § 201.57(c)(6), the Warnings and Precautions section of prescription drug labels must “describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification).”⁶⁷

68. A manufacturer “must periodically submit any new information that may affect the FDA’s previous conclusions about the safety, effectiveness, or labeling of the drug.”⁶⁸

69. The U.S. Supreme Court has reaffirmed this responsibility: “It has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market. See, *e.g.*, 21 CFR § 201.56 (requiring manufacturer to provide labeling that contains a “summary of essential scientific information needed for the safe and effective use of the drug,” and “be informative and accurate and neither promotional in tone nor false or misleading in any particular”); 21 CFR § 201.80(e) (requiring a manufacturer to revise its label “to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug”); § 314.80(b) (placing responsibility for post-marketing surveillance on the manufacturer); 73 Fed.Reg. 49605 (‘Manufacturers continue to have a responsibility under Federal law ... to maintain their labeling and update the labeling with new safety information’).” *Wyeth v. Levine*, 555 U.S. 555 (2009).

⁶⁷ 21 C.F.R. § 201.57(c)(6) (emphasis added).

⁶⁸ *Wyeth v. Levine*, 555 US 555 (2009) at 608, citing 21 U.S.C. § 355(k).

70. As I have written in an article co-authored with David Vladek: “In fact, drug manufacturers have significant authority — and indeed a responsibility — to modify labeling when hazards emerge and may do so without securing the FDA’s prior approval.”⁶⁹

71. In many instances, safety issues arise after a drug is on the market. It is the responsibility of the manufacturer to identify, analyze, assess, evaluate, and inform physicians and patients about such safety risks.⁷⁰

72. Sanofi recognizes this responsibility. It’s vice-president and head of global regulatory affairs for North America testified:

Q. Okay. Do you agree that a drug manufacturer has an ongoing obligation to make sure that its labeling accurately reflects the company’s current knowledge concerning the common risks posed by its drug?

A. Yes, I do.⁷¹

73. Sanofi’s global safety officer for Taxotere from May 2006 to December 2013 stated:

A. . . . If I know that a certain risk, it’s inherent to my drug, I have the obligation to state how it can be minimized, how patients can take my drug and either not having that risk or having it at tolerable levels.⁷²

74. Sanofi’s Senior Manager for labeling for oncology products in the U.S. regulatory affairs department from June 2013 to October 2016 testified:

Q. Do you agree that a drug manufacturer must provide informative and accurate information in its label to effectively communicate with doctors?

⁶⁹ Kessler D., Vladeck D. (2008). A Critical Examination of the FDA’s Efforts to Preempt Failure-to-Warn Claims, 96 Geo. L.J. 461

⁷⁰ *See id.*

⁷¹ Deposition of Sunil Gupta, M.D., FRCPC, dated April 10, 2018, at 26:7-12. *See also* Schedule 6, Sanofi Employees and Personnel Cited or Referenced in Report.

⁷² Deposition of Emanuel Palatinsky, M.D., dated August 9, 2018, at 65:19-23.

- A. Yes, and they do that by constant monitoring of the product. You know, the label is a living document that is constantly changing over its life -- lifecycle.⁷³

75. The Food, Drug, and Cosmetic Act requires drug manufacturers to provide adequate warnings about a drug. 21 U.S.C. 352 states: “A drug or device shall be deemed to be misbranded—(a) False or Misleading Label: If its labeling is false or misleading in any particular....(f) Directions for use and warnings on label: Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users...(j) Health-endangering when used as prescribed: If it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.” (Emphasis added).

76. The supplemental applications to market a new drug submitted by Sanofi to the FDA⁷⁴ include a certification signed by a Sanofi-responsible official stating: “I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. . . . I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following: . . . 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.”⁷⁵

77. FDA regulations also require that new information be reported in periodic and annual reports. 21 CFR 314.81(b)(2)(i) states: “Summary: A brief summary of significant new

⁷³ Deposition of Frances Polizzano, PharmD, dated February 28, 2018, at 28:6-17 (objection omitted).

⁷⁴ As discussed above in Section III of this Report, Sanofi submitted supplemental NDAs for new indications for Taxotere at various times.

⁷⁵ Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use (21 CFR 314 & 601).

information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of the actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study.”⁷⁶

78. If a drug manufacturer states on the label that a drug has risks that are similar to other drugs in its class, but in fact there are scientific data that indicate that the drug has increased risk compared to other drugs in the class, that label would be false or misleading under the Food, Drug, and Cosmetic Act.

V. KEY DEFINITIONS

79. The National Cancer Institute at the National Institutes of Health defines alopecia as “[t]he lack of hair from areas of the body where hair is usually found. Alopecia can be a side effect of some cancer treatments.”⁷⁷

80. According to a Sanofi leaflet distributed to healthcare providers, alopecia “is another word for hair loss or thinning of the hair. It is a common, yet temporary, side effect of some cancer medicines. Alopecia can occur anywhere on the body and may happen after a few treatments.”⁷⁸

81. With respect to irreversible alopecia, the medical literature has generally defined this condition as the “complete loss of growth or partial regrowth at least 6 months after chemotherapy.”⁷⁹

⁷⁶ *Id.*

⁷⁷ National Cancer Institute Diction of Cancer Terms, *available at* <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/alopecia> (last visited Sep. 21, 2016).

⁷⁸ (Sanofi_01038470 at 5).

⁷⁹ *See, e.g.,* Kim G, Kim S, Park H. et al. (2017). Chemotherapy-induced irreversible alopecia in early breast cancer patients. *Breast Cancer Res Treat* 163:527-533; Namini S. (2016). Systematic Review of the Risk of Permanent Alopecia with Docetaxel Treatment for Breast Cancer. *J Clin Case Rep* 6(8); Haider M, Hamadah I, Almutawa A.

82. Over the last decade, Sanofi has defined irreversible alopecia multiple ways.

83. In an email dated March 16, 2010 regarding the social media communication plan for Taxotere, Sanofi’s Global Safety Officer, Dr. Emanuel Palatinsky, wrote it was reasonable to consider alopecia permanent if the alopecia lasted for more than four years following treatment with Taxotere.⁸⁰

84. In Sanofi’s Periodic Safety Update Report (“PSUR”) dated January 18, 2011, Sanofi attached Appendix 13 titled “Clinical Overview Docetaxel – Persistent Alopecia,” which defined “persistent alopecia” as “alopecia nor[sic] recovered after 12 months from the end of a chemotherapy regimen than included docetaxel.”⁸¹

85. Sanofi subsequently changed its definition, stating that irreversible alopecia is “alopecia lasting more than 2 years”⁸² in response to a March 23, 2015 request by FDA for a summary of irreversible alopecia cases associated with Taxotere use.⁸³

VI. IRREVERSIBLE ALOPECIA MEETS FDA CRITERIA OF “SERIOUS” AND/OR “CLINICALLY SIGNIFICANT”

86. As noted above, under FDA regulations, the Warnings and Precautions section of drug labels must include serious and/or clinically significant adverse events”⁸⁴

(2013). Radiation- and Chemotherapy-Induced Permanent Alopecia: Case Series. *J Cutaneous Med & Surgery* 17(1):55-61; Kluger N, Jacot W, Frouin E. et al. (2012). Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/ epirubicin/ cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients. *Annals of Oncology* 23(11):2879-2884; Tallon B. Blanchard E. Goldberg L. (2010). Permanent chemotherapy-induced alopecia: Case report and review of the literature. *J Am Acad Dermatol* 63:333-6; *see also* Sanofi_01021777 at 1.

⁸⁰ (Sanofi_05252079 at 2); *see also* Emanuel Palatinsky, M.D. Dep. 443:15-445:09.

⁸¹ (Sanofi_00197757 at 8); (Sanofi_01397018 at 2); (Sanofi_05059757 at 1); Emanuel Palatinsky, M.D. Dep. 291:16-294:09.

⁸² (Sanofi_04878450 at 4; *see also* (Sanofi_01021777 at 1); (Sanofi_00800098 at 3); (Sanofi_02664951); (Sanofi_01268180 at 35).

⁸³ (Sanofi_04878450 at 7); (Sanofi_01268180 at 8).

⁸⁴ 21 C.F.R. § 201.57(c)(6).

87. FDA’s 2011 Guidance on Warnings in labeling directs “The WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or are *otherwise clinically significant* because they have implications for prescribing decisions or for patient management.”⁸⁵

88. According to 21 C.F.R. § 314.80, a serious adverse drug experience includes the following outcomes: “death; a life-threatening adverse event; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or a congenital anomaly or birth defect.”⁸⁶

89. FDA’s Guidance also states, “Adverse reactions that do not meet the definition of a serious adverse reaction, but are otherwise clinically significant because they have implications for prescribing decisions or patient management, should also be included in the WARNINGS AND PRECAUTIONS section.”⁸⁷

90. In determining if an adverse reaction is otherwise clinically significant, the drug’s indication (i.e. the relative seriousness of the disease or condition treated)⁸⁸ and the incidence of an adverse reaction should be considered.⁸⁹

⁸⁵ FDA Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products (2011), at 3, available at <https://www.fda.gov/downloads/drugs/guidances/ucm075096.pdf>.

⁸⁶ *Id.* at 3; *see also* 21 C.F.R. § 314.80.

⁸⁷ FDA 2011 Guidance for Industry, at 4.

⁸⁸ FDA’s Guidance states:

The relative seriousness of the disease or condition treated should be considered. For example, non-serious adverse reactions (e.g., nausea, pruritis, alopecia) caused by drugs intended to treat minor, self-limiting conditions (e.g., allergic rhinitis, cosmetic conditions, transient insomnia) may be considered clinically significant. However, those same adverse reactions caused by drugs intended to treat serious or life-threatening conditions (e.g., cancer) may be considered much less clinically significant and not appropriate for inclusion in this section.

91. With respect to incidence, the FDA’s Guidance provides, “A high absolute risk or rate of occurrence of an adverse reaction can be a factor in deciding whether to include the reaction in this section.”⁹⁰

92. FDA instructs that the following adverse reactions could be considered otherwise clinically significant:

(1) an adverse reaction that may lead to a potentially serious outcome unless the dosage or regimen is adjusted, the drug is discontinued, or another drug is administered to prevent the serious outcome; (2) an adverse reaction that could be prevented or managed with appropriate patient selection, monitoring, or avoidance of concomitant therapy, and prevention or management of the adverse reaction is needed to avoid a potentially serious outcome; (3) an adverse reaction that can significantly affect patient compliance, particularly when noncompliance has potentially serious consequences.⁹¹

93. The medical literature discussing alopecia and irreversible alopecia (including not just scalp hair, but also loss of eyebrows, eyelashes, and hair in other body regions) describes the distressing nature of this injury and its profound impact on mental health, physical, psychosocial and psychological distress, quality of life, patient compliance, and patient willingness to undergo chemotherapy or instead choose a different therapy or treatment.⁹²

Id. at 4. FDA’s Guidance does not discuss how the adverse reaction of irreversible alopecia may be considered. FDA’s Guidance does not provide that consideration of indication limits an analysis of other factors and examples provided in its Guidance, including but not limited to, incidence and affect on potential compliance.

⁸⁹ *Id.*

⁹⁰ *Id.* at 4.

⁹¹ *Id.*

⁹² Kang D. (2018). Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study. *The Oncologist* 23:1-7 (“Similar to the results of previous studies, patients with PCIA [permanent chemotherapy-induced alopecia] had much worse body image than patients without PCIA. In previous studies, patients with worse body image were more likely to have depression, lower social and role functioning, problems with sexuality, and poorer quality of life.”); Davis D.S. (2017). Review of quality of life studies in women with alopecia. *International Journal of Women’s Dermatology* 4:18-22 (“Alopecia has been shown in multiple studies to have a psychosocial impact in both men and women; however, the impact may be more severe and devastating in women. The psychological burden of hair loss in women is significant and should not be overlooked. Both scarring and nonscarring forms of alopecia have been shown to have a negative impact on QoL.”); Kim G. (2017). Chemotherapy-induced irreversible alopecia in early breast cancer patients. *Breast Cancer Res Treat*

published online at doi:10.1007/s10549 017 4204 x) (“Chemotherapy-induced alopecia (CIA) is very common and causes a severe stress to these potentially curable female patients. It does affect not only sociological function of the patients but also tribute a physical and psychological distress to these women leading to low self-esteem and low quality of life.”); Smith K. (2017). Madarosis: a qualitative study to assess perceptions and experience of Australian patients with early breast cancer treated with taxane-based chemotherapy. Support Care Center DOI 10.1007/s00520-017-3852-z (“Our data suggests that chemotherapy-induced madarosis may result in a range of psychological issues of importance. It also indicates physical side effects of dry eye and irritation can occur. . . . Many women struggled with the perceived change of appearance associated with madarosis. The women in this study felt that their physical attractiveness was lessened by the presence of madarosis and experienced distress. There was a clear message that the loss of eyelashes and eyebrows resulted in personal identification with the sick or cancer role.”); Rice B. (2017). Registry study to assess hair loss prevention with the Penguin Cold Cap in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat DOI 10.1007/s10549-017-4506-z (“CIA has been shown to affect female breast cancer patients who report loss of self-confidence and increased concern over being publicly identified as a cancer patient. Complete alopecia is a reminder to the patient and others of her disease, and patients have reported negative effects on self-image, quality of life, and normal social and professional functioning.”); Rencz F. (2016). Alopecia areata and health-related quality of life: a systematic review and meta-analysis. Br J Dermatol 175(3):561-571 (“Patients with AA [alopecia areata] experience significant impairment in HRQOL [health-related quality of life], especially in the area of mental health.”); Rossi A. (2016). Chemotherapy-induced alopecia management: Clinical experience and practical advice. J Cosmet Dermatol 2017:1-5 (“Chemotherapy-induced alopecia (CIA) is probably one of the most shocking aspects for oncological patients and underestimated by physicians. It negatively influences body image, sexuality, and self-esteem, so that up to 8% of patients decide to refuse chemotherapy if there is the risk of hair loss.”); Shilpashree P. (2016). Impact of female pattern hair loss on the quality of life of patients. Journal of Pakistan Association of Dermatologists. 26(4):347-352 (“Hair loss in women is associated with significant psychological morbidity. Societal norms dictate that hair is an essential part of a woman’s sexuality and gender identity, and any hair loss generates feelings of low self-esteem and anxiety from a perception of diminished attractiveness. Women are more likely than men to have a lowered quality of life and to restrict social contacts as a result of hair loss.”); Sibaud V. (2016). Dermatological adverse events with taxane chemotherapy. Eur J. Dermatol (26(5): 427-443) (“It is imperative that patients are forewarned of the potential for CIPAL [Chemotherapy-induced persistent alopecia] with taxanes, for ethical and medico-legal reasons. This is particularly true in the adjuvant treatment setting, especially in the female breast cancer population, where the overall prognosis is generally good and patients are younger.”); Trusson D. (2016). The Role of Hair Loss in Cancer Identity. Cancer Nursing Vol. 39, No. 4 (“[H]air loss as a result of chemotherapy treatment for breast cancer can have profound implications for women’s mental health and social interactions.”); Lewis-Smith H. (2015). Physical and psychological scars: The impact of breast cancer on women’s body image. Journal of Aesthetic Nursing 4(2):80-83 (“Hair holds meaningful value across many cultures, reflecting beauty, gender, age, and religious affiliations, whilst being associated with personal growth and life (Batchelor, 2001; Freedman, 1994). Hair loss is also a traumatic experience and can impose detrimental and long-lasting impacts on body image, sexuality and self-concept (Batchelor, 2001; Münstedt et al., 1997). In fact, women with breast cancer often consider scalp hair loss as the most distressing appearance-altering side effect of chemotherapy treatment, followed by the loss of eyebrows and loss of eyelashes (Nozawa et al., 2013). One study found that body satisfaction which dropped during treatment, failed to improve to pre-treatment levels when the hair started to grow back (Münstedt et al., 1997). The loss of hair is often experienced more negatively than the loss of a breast, with hair considered integral in the sense of identity and its loss representing a visible reminder of the cancer, leaving the person to feel like a “cancer patient” (Browall et al., 2006; Freedman, 1994).”); Pavey R. (2015). Dermatological adverse reactions to cancer chemotherapy. Indian J Dermatol Venereol Leprol 2015;81:434 (“Hair loss has been rated as one of the most distressing side effects of chemotherapy, along with vomiting and nausea. There have been reports of refusal of chemotherapy, especially among women, because of the risk of hair loss.”); Choi E. (2014). Impact of chemotherapy-induced alopecia distress on body image, psychosocial well-being, and depression in breast cancer patients. Psycho-Oncology 23(1103-1110) (“Among side effects, alopecia is considered one of the most traumatizing and distressing experiences for women with breast cancer. Often, losing hair has been described as a harder experience than losing breasts, and some patients refuse chemotherapy because of the expected hair loss.”); Thorp N. (2014). Abstract P5-17-04: Long term hair loss in patients with early breast cancer receiving docetaxel chemotherapy. Presented at the Annual San Antonio Breast Cancer Symposium, December 9-13, 2014 (“Long term hair loss had a significant impact on quality of survival. This is an important quality of life issue for patients which

merits prospective study to confirm incidence, to identify effective preventive and management strategies. This risk should be discussed routinely (as part of the process of informed consent) with all patients embarking on docetaxel as a component of management of EBC [early breast cancer].”); Van den Hurk C.J.G. (2014). Measurement of chemotherapy-induced alopecia—time to change. Support Care Center DOI 10.1007/s00520-015-2647-3 (“For breast cancer patients, the impact of CIA is much higher than expected by MDs and nurses.”); Villasante A. (2014). Chemotherapy-Induced Alopecia. *J Clin Investigat Dermatol* 2014;2(2):8 (“Alopecia makes patients aware of their own vulnerability and serves as a constant reminder of illness and mortality. About half with CIA [chemotherapy-induced alopecia] believe that their cancer diagnosis is obvious to everyone around them despite camouflage with wig use. Patients mention not only the loss of scalp hair, but also the loss of eyebrows and eyelashes, as particularly conspicuous. . . . In a pretreatment survey of female breast cancer patients, 8.3% felt so distressed by the likelihood of CIA that they would consider declining chemotherapy. In a 1997 study, 46.6% of patients cited CIA as the single most traumatic side effect of cancer therapy.”); Bertrand M. (2013). Abstract P3-09-15: Permanent chemotherapy induced alopecia in early breast cancer patients after (neo)adjuvant chemotherapy: Long term follow up. Thirty-Sixth Annual CTRC-AACR San Antonio Breast Cancer Symposium, Dec. 10-14, 2013 (“The presence of impaired quality of life was significantly higher in the group alopecia than in the control group ($p=0.00006$).”); Can G. (2013). A comparison of men and women’s experiences of chemotherapy-induced alopecia. *European Journal of Oncology Nursing* 15:255-260 (“The visual nature of alopecia can affect the body image, quality of life, social interaction and sexuality of the patient (Randall and Ream, 2005). It may seriously affect body image, which in turn has an impact on self-esteem and self-confidence. Consequently, it may cause emotional suffering, may lead to personal, social and work-related problems, and may have a negative effect on quality of life (Auvien et al., 2010; Cartwright et al., 2008; Christodoulou et al., 2002; Hunt and McHale, 2005; Hurk et al., 2010).”); Cho J. (2013). Development and validation of Chemotherapy-induced Alopecia Distress Scale (CADS) for breast cancer patients. *Annals of Oncology* 00:1-6 (“Overall, research suggests that chemotherapy-induced alopecia (CIA) significantly impacts QOL and psychosocial adjustment among breast cancer patients.”); Jayde V. (2013). The experience of chemotherapy-induced alopecia for Australian women with ovarian cancer. *European Journal of Cancer Care* 22:503-512 (“Chemotherapy-induced alopecia is frequently described as one of the most distressing aspects of treatment for cancer (Freedman 1994; Munstedt *et al.* 1997; Carelle *et al.* 2002; Rosman 2004; Hansen 2007; Lemieux *et al.* 2008; Power & Condon 2008; Trueb 2009; Borsellino & Young 2011; Chon *et al.* 2012). Alopecia has been linked to changes in self-concept and body image (Munstedt *et al.* 1997; Williams *et al.* 1999; Hesketh *et al.* 2004). ‘Throughout history, hair has been symbolic of the social, cultural, and political climate’ (Munstedt *et al.* 1997, p. 140). In western society, glossy healthy looking hair on women is viewed as being desirable and symbolizing femininity. Women typically ‘do’ their hair each morning, as part of preparation of their external self for the day ahead (Cash 2001).”); Chon S. (2012). Chemotherapy-induced alopecia. *J Am. Acad Dermatol* 2012;67:e37-47 (“Across the literature, hair loss consistently ranks among the most troublesome and traumatic aspects of chemotherapy. . . . Some women have found hair loss to be more difficult to cope with than the loss of a breast. Others have considered refusing treatment because of anticipated alopecia. These strong reactions may reflect the importance of hair in self-identity.”); Kim I. (2012). Perception, Attitudes, Preparedness and Experience of Chemotherapy-Induced Alopecia among Breast Cancer Patients: a Qualitative Study. *Asian Pacific J Cancer Prev* 13:1384-1388 (“Alopecia is one of the most painful side effects of chemotherapy, and it often ranks among the first three most important side effects for breast cancer patients (Sitzi and Huggins, 1998; Duric et al., 2005; Lemieux et al., 2008). Chemotherapy-induced alopecia has a strong negative impact self-image (Baxley et al., 1984; Hunt and McHale, 2005), shame feeling (Auvinen et al., 2010), and perception of aging and body image (Baxley et al., 1984; Fobair et al., 2006), resulting in reduced quality of life in breast cancer patients (Rosman, 2004; Cartwright et al., 2009). . . . If baldness represented being sick, new hair after alopecia represented hope and renewed life. Many participants said that they felt that hardship was over when they saw newly growing hair and that that looking at new hairs made them feel alive and happy. All participants said that they recognized again the importance of their lives. . . . We found that breast cancer patients experienced a variety of psychosocial problems related to alopecia, and the resulting distress interfered with social activities and interactions, including their willingness to continue working or returning to work. In addition, the range of physical problems due to alopecia reported in our study was broader than the problems reported in the literature and were not limited to the head or scalp but also to the nose, eyes, and other body hair.”); Kluger N. (2012). Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients. *Annals of Oncology* 23:2879-2884; Koszalinski R. (2012). Embodying Identity in Chemotherapy-Induced Alopecia. *Perspectives in Psychiatric Care* 48:116-121; Zannini L. (2012). My wig has

been my journey's companion': perceived effects of an aesthetic care programme for Italian women suffering from chemotherapy-induced alopecia. *European Journal of Cancer Care* DOI: 10.1111/j.1365-2354.2012.01337.x ("A recent study reported that 47% of female patients consider hair loss to be the most traumatic aspect of chemotherapy (Trüeb 2010). Chemotherapy-induced alopecia can cause the development of a negative body image, lowered self-esteem, and a reduced sense of well-being (Hesketh *et al.* 2004). Hair is indeed a symbol of life and identity, and in many cultures, it is perceived as an element characteristic of a woman's femininity (Freedman 1994; McGarvey *et al.* 2001). Hair loss can be associated with the condition of sickness, and alopecia is considered to be a constant reminder of the presence of cancer (Williams *et al.* 1999; Batchelor 2001). Furthermore, as noted by Freedman (1994), 'for many, across cultures and religious groups, the meaning of the shaved head, can be symbolic of the state of disgrace, which becomes a stigmata of sin or wrongdoing' (Freedman 1994, p. 337)."); Bernard M. (2011). Perception of alopecia by patients requiring chemotherapy for non-small-cell lung cancer: A willingness to pay study. *Lung Cancer* 72:114-118 ("Hair loss is reported to be one of the most traumatic effects of chemotherapy, affecting both body image and self-perception. Alopecia has been cited as the most feared side effect by up to 58% of women preparing for chemotherapy, and some patients may avoid treatment for this reason. Women with cancer who experience alopecia report lower self-esteem, poorer body image, and lower quality of life."); Breed R. (2011). Presentation, Impact and Prevention of Chemotherapy-induced Hair Loss. *Expert Rev Dermatol* 6(1):109-125 ("For some patients, CIA is a reason to refuse chemotherapy, and as much as 8% of patients may choose chemotherapy regimens with possibly less favorable tumor outcomes as long as these regimens do not cause severe hair loss."); Miteva M. (2011). Permanent Alopecia After Systemic Chemotherapy: A Clinicopathological Study of 10 Cases. *Am J Dermatopathol* 33:345-350 ("The psychological impact of chemotherapy-induced alopecia (CIA) is of prime concern among patients receiving chemotherapy, particularly women. One survey demonstrated that 47% of female cancer patients consider CIA the most traumatic aspect of chemotherapy, and 8% would even decline chemotherapy because of this fear of hair loss."); Roe H. (2011). Chemotherapy-induced alopecia: advice and support for hair loss. *British Journal of Nursing* Vol. 20, No. 10 ("Many women have reported that their hair loss was the most traumatic psychological side effect they faced while receiving chemotherapy (McGarvey *et al.* 2001), the third worse overall side effect they experienced after nausea and vomiting (Munstedt *et al.* 1997), and the one that added to the distress of their original diagnosis (McGarvey *et al.* 2001)."); Yeager C. (2011). Treatment of chemotherapy-induced alopecia. *Dermatologic Therapy* Vol. 24:432-442 ("Although not life threatening, hair loss continues to be one of the most distressing and troublesome side effects of chemotherapy for patients. In his study of women undergoing treatment for primary breast cancer, Freedman found that some women refused chemotherapy because of the risk of developing hair loss. Likewise, Tierney and colleagues found that 8% of the women in their study considered refusing chemotherapy because of the risk of chemotherapy-induced alopecia."); Corina J. (2010). Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psycho-Oncology* 19:701-709 ("Alopecia may seriously affect one's body image, which in turn has an impact on self-esteem and self-confidence. Consequently, it may cause emotional suffering, may lead to personal, social and work related problems and may have a negative effect on quality of life."); Masidonski P. (2009). Permanent Alopecia in Women Being Treated for Breast Cancer. *Clinical Journey of Oncology Nursing* Vol. 13, No. 1 ("Alopecia is a devastating diagnosis for women and men, regardless of the cause. Hair can reveal aspects of self, health, ethnicity, and socioeconomic status. Self-esteem and confidence are negatively affected in patients who experience hair loss."); Prevezas C. (2009). Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *British Journal of Dermatology*; 160:881-898 ("Explaining and preventing such complications is very important as the possibility of developing irreversible alopecia plays a major role in a patient's decision regarding the proposed chemotherapy regimen."); Trueb R. (2009). Chemotherapy-Induced Alopecia. *Semin Cutan Med Surg* 28:11-14 ("Few dermatologic conditions carry as much anxiety and emotional distress as hair loss resulting from chemotherapy-induced alopecia (CIA). CIA is considered one of the most traumatic factors in cancer patient care and occurs with an estimated incidence of 65%. Hair loss negatively affects a patient's perception of appearance, body image, sexuality, and self-esteem. Moreover, patients feel deprived of their privacy because the hair loss is readily interpreted by the lay public as associated with having cancer. Women are particularly affected. A survey demonstrates that 47% of female cancer patients consider CIA the most traumatic aspect of chemotherapy, and 8% would even decline chemotherapy because of this fear of hair loss."); Power S. (2008). Chemotherapy-induced alopecia: a phenomenological study. *Cancer Nursing Practice*, Vol. 7, No. 7 ("Alopecia is one of the most distressing and visually noticeable effects of cancer treatment. For some patients, the fear of treatment-induced alopecia is so significant that some women may refuse potentially curative chemotherapy."); Lemieux J. (2008). Chemotherapy-induced alopecia and effects on quality of life among women with breast cancer: a literature review.

Psycho-Oncology 17:317-328 (“[C]hemotherapy-induced hair loss is considered to be the most important side effects of chemotherapy, frequently ranking among the first three for breast cancer patients and can lead to refusal of chemotherapy. Secondly, it is described by breast cancer women as causing distress and as being traumatizing.”); Harcourt D. (2008). Women’s Experiences of an Altered Appearance during Chemotherapy: An Indication of Cancer Status. *J Health Psychol* 13:597 (“Previous research into the psychological impact of chemotherapy has reported patients ranking hair loss as the second most severe side-effect of treatment (Carelle et al., 2002). Our findings support those of Rosman (2004) in demonstrating that it is the outward changes that publicly identified participants as having cancer and as a consequence, presented them with an additional array of potential stressors. In essence their appearance acts as a visible indicator of their disease status to both themselves and others, including those who may have previously been unaware of it. Hair loss is seen as a confirmation of identity as a cancer patient (Rosman, 2004).”); Firth H. (2007). Anticipating an altered appearance: Women undergoing chemotherapy treatment for breast cancer. *European Journal of Oncology Nursing* 11, 385-391 (“Alopecia or hair loss is often rated as one of the most common, feared, and traumatic aspects of chemotherapy and may even be considered emblematic of the treatment and of cancer itself.”); Hansen H. (2007). Hair Loss Induced by Chemotherapy: An Anthropological Study of Women, Cancer and Rehabilitation. *Anthropology & Medicines* Vol. 14, No. 1:15-26; Wang J. (2006). Protection against chemotherapy-induced alopecia. *Pharmaceutical Research*, Vol. 23, No. 11 (“Alopecia negatively affects a patient’s perception of physical appearance, body image, sexuality and self-esteem, and deprives patients of the privacy of having cancer. Chemotherapy-induced alopecia (CIA) is considered one of the most negative factors in cancer patient care. The National Coalition for Cancer Survivorship cites CIA as one of the most emotionally upsetting aspects of coping with cancer. Female patients are particularly affected; a survey shows that 47% patients consider CIA the most traumatic side effect of chemotherapy, and 8% would reject chemotherapy due to fear of CIA. Alopecia also results in reduced social interactions in school-age children and teenagers. The negative psychological impact of CIA may have additional undesirable biological consequences, as depression lowers immune function and is associated with cancer progression.”); Sedlacek SW, Persistent Significant Alopecia (PSA) form Adjuvant Docetaxel after Doxorubicin/Cyclophosphamide (AC) Chemotherapy in Women With Breast Cancer. Presented at the Annual San Antonio Breast Cancer Symposium, December 14-17, 2006 (“Such an emotionally devastating long term toxicity from this combination must be taken into account when deciding on adjuvant chemotherapy programs in women who will likely be cured of their breast cancer.”); Hunt N. (2005). The psychological impact of alopecia. *British Med. J.* 331:951-3 (“Such evidence as exists supports the view that the experience of alopecia is psychologically damaging, causes intense emotional suffering, and leads to personal, social, and work related problems. There is an important link between hair and identity, especially for women. About 40% of women with alopecia have had marital problems as a consequence, and about 63% claim to have had career related problems. The extent of alopecia is one of the predictors of psychological distress. People with severe hair loss are more likely to experience psychological distress.”); Luoma M. (2004). The meaning of quality of life in patients being treated for advanced breast cancer: a qualitative study. *Psycho-Oncology* 13:729-739 (“Changes in appearance occurred more often in the docetaxel group, with altered body image including instances of alopecia and oedema. Patients reported alopecia as a distressing side effect. Changes in appearance often led to limitations in social functioning, influencing the patients’ willingness to go outdoors, visit other people and continue employment. Many patients felt that they did not want to go outdoors, because strangers would become aware of their illness by noticing them wearing a wig”); Hesketh P. (2004). Chemotherapy-induced alopecia: psychosocial impact and therapeutic approaches. *Support Care Center* 12:543-49 (“The impact of hair loss can be enormous. For some women, hair loss can have more of an impact than a mastectomy. Others are so distressed at facing the prospects of losing their hair that they may choose less effective therapies or opt for no treatment at all. CIA can cause anxiety, depression, negative body image, lowered self-esteem, and a reduced sense of well-being.”); Batchelor D. (2001). Hair and cancer chemotherapy: consequences of nursing care – a literature study. *European Journal of Cancer Care* 10:147-163 (“When patients experience hair loss, they experience many thoughts and feelings such as anger, sadness, embarrassment and fear of rejection (Chernecky 1983).”); McGarvey E. (2001). Psychological Sequelae and Alopecia Among Women with Cancer. *Cancer Practice* Nov./Dec. 2001, Vol. 9, No. 6 (“Alopecia is a prime concern of women with cancer, so much so that it may influence their choice of or agreement to consent to potentially lifesaving treatments.”); Williamson D. (2001). The effect of hair loss on quality of life. *J Eur Acad Dermatol Venereol* 2001 Mar., 15(2):137-9 (“This study specifically identifies the feelings of loss of self-confidence, low self-esteem and heightened self-consciousness in people affected by hair loss.”); Munstedt K. (1997). Changes in self-concept and body image during alopecia induced cancer chemotherapy. *Support Care Cancer* 5:139-143 (“Especially in women, hair is a part of the identity and sense of self. Loss of hair due to cancer

94. Sanofi recognizes the serious and significant nature of irreversible alopecia and its potential impact on patient compliance and patient willingness to undergo a particular chemotherapy or instead choose a different therapy or treatment.

94.1. Sanofi's global safety officer for Taxotere from May 2006 to December 2013 stated:

- a. What I was telling you is that the impact of losing part of the hair permanently, a slight hair loss, could be much more severe or felt more severely from a patient than losing the entire amount of hair only for a partial -- for a part of a time. That's what I was saying.⁹³

94.2. Sanofi's vice-president and head of global regulatory affairs for North America testified:

Q. Do you agree that permanent alopecia or irreversible alopecia can cause serious psychological consequences in the women who are affected by it?

A. Yes. That, I think, would be disturbing for women, yes.

...

Q. When you were preparing and working on the label for Taxotere, did you ever consider the serious psychological effects of permanent alopecia on women?

A. Yes, I think I mentioned even in an earlier testimony that we don't take these things lightly. Psychological effects are important, aesthetic aspects are important, so we do not take this lightly.⁹⁴

chemotherapy has been proven to alter patients' body image and self-concept, resulting in altered social behavior and a higher degree of depression and anxiety."); Tierney A. (1992). Knowledge, Expectations and Experiences of Patients receiving Chemotherapy for Breast Cancer. *Scand J. Caring Sci*, Vol. 6, No. 2 ("Of the side-effects mentioned, each patient was asked which she anticipated would be, for her, the most difficult to cope with. Hair loss was most frequently cited, this being expected. as the most difficult side-effect by 35 patients (58.3%) in the sample. A small number of patients ($n = 5$, 8.3%) admitted to having been so distressed by the prospect of hair loss as to consider refusing the treatment."); Coates A. (1983). On the Receiving End—Patient Perception of the Side-effects of Cancer Chemotherapy. *Eur J Cancer Clin Oncol.*, Vol. 19, No. 2:203-208. *See also* Schedule 5, Studies Regarding the Risk of Irreversible Alopecia Associated with Taxotere and Details of Other Studies Cited or Referenced in This Report.

⁹³ Deposition of Emanuel Palatinsky, M.D., dated August 9, 2018, at 180:19-25.

⁹⁴ Deposition of Sunil Gupta, M.D., FRCPC, dated April 10, 2018, at 103:10-16, 104:7-16 (objections omitted).

94.3. In 2007, Sanofi internally circulated a “Taxotere Lung Cancer Transmission” summarizing a 2005 article from Dubey titled “Patient Preferences in Choosing Chemotherapy Regimens for Advanced Non-Small Cell Lung Cancer” published in The Journal of Supportive Oncology.⁹⁵ The internal transmission included a bolded footer stating “**For Background Information Only. Do Not Duplicate, Distribute, or Use in Promotion.**”⁹⁶ Under “Key Findings,” Sanofi wrote: “In this study, 90% of women were concerned about alopecia; 11% would consider refusing treatment that may result in hair loss; This is similar to results of breast cancer questionnaires.”⁹⁷

94.4. In July 2009, Sanofi sponsored a clinical trial with a stated primary objective/endpoint described as “Rate of complete chemotherapy induced alopecia (WHO grade III or IV, physician grading).”⁹⁸ The publication co-authored by Sanofi after completion of its study stated:

Chemotherapy-induced alopecia is very distressing for a patient and may have an impact on treatment decisions. On docetaxel-based therapy, alopecia occurs in a substantial proportion of patients.

. . .

For many patients, alopecia is emotionally extremely distressing, causing traumalike fears and anxieties, depression, reduced self-esteem, and reduced willingness to undergo cancer therapy.⁹⁹

⁹⁵ (Sanofi_01039954) (summarizing Dubey S. (2005). Patient Preferences in Choosing Chemotherapy Regimens for Advanced Non-Small Cell Lung Cancer. The Journal of Supportive Oncology 3(2):149-154.

⁹⁶ *Id.*

⁹⁷ *Id.*

⁹⁸ See Sanofi-sponsored clinical trial at <https://clinicaltrials.gov/ct2/show/NCT01008774>. Secondary objectives included: (1) compliance to scalp cooling procedure; (2) received number of cycles of chemotherapy in each subgroup; (3) patient perception of scalp cooling procedure; and (4) side effects of scalp cooling systems.

⁹⁹ Betticher D. (2013). Efficacy and tolerability of two scalp cooling systems for the prevention of alopecia associated with docetaxel treatment. Support Care Cancer (2013) 21:2565-2573. See also excerpts from Sanofi Periodic Safety Reports labeling irreversible alopecia as a “serious” condition (*e.g.*, Sanofi_00181652, Sanofi_00181660, Sanofi_00181671, Sanofi_00182055).

95. Regulatory authorities have concluded and corresponded with Sanofi regarding the serious and significant nature of irreversible alopecia.

95.1. On June 29, 2011, the European Medicines Agency (EMA) advised Sanofi that “Given the serious psychological consequences of this adverse effect in, often young, patients treated mainly in the adjuvant scheme, Health care professionals and patients should be informed of the possible irreversibility of alopecia.”¹⁰⁰

95.2. In correspondence dated March 2011, the French Agency for the Safety of Health Products (AFSSAPS) provided Sanofi with the same conclusion as EMA.¹⁰¹

95.3. In a report dated March 2018 from FDA and Center for Drug Evaluation and Research (CDER) as part of FDA’s Patient-Focused Drug Development Initiative, FDA and CDER stated, “The perspectives shared by participants, both adult and pediatrics, at this meeting provided a vivid examination of the challenges and burdens facing patients with alopecia. These discussions clearly conveyed that alopecia areata can have a debilitating emotional and psychological impact on patients which goes beyond the loss of hair.”¹⁰²

96. I also reviewed data from the medical literature¹⁰³ and Sanofi’s clinical trials regarding the incidence rate or rate of occurrence for irreversible alopecia associated with Taxotere.

96.1. The medical literature provides an incidence rate or rate of occurrence ranging from 6.3% - 10.06% (or higher).¹⁰⁴

¹⁰⁰ (Sanofi_04864365).

¹⁰¹ (Sanofi_02540992).

¹⁰² FDA and CDER, Voice of the Patient: Alopecia Areata, March 2018.

¹⁰³ A more detailed review of the medical literature regarding irreversible alopecia is set forth below and in Schedule 5, Studies Regarding the Risk of Irreversible Alopecia Associated with Taxotere and Details of Other Studies Cited or Referenced in This Report.

96.2. The 2004 interim data and 2009 final data from two of Sanofi's clinical trials (TAX 316 and TAX 301/GEICAM 9805) provide an incidence rate or rate of occurrence ranging from 3.2% to 9.2%.¹⁰⁵ Sanofi referenced these incidence rates or rates of occurrence in internal presentations and email correspondence, in responses to correspondence and requests for information from foreign regulatory authorities, and in certain Summaries of Product Characteristics provided in Europe.¹⁰⁶

97. In my opinion, irreversible alopecia meets the criteria for seriousness or otherwise clinically significant.

VII. METHODOLOGY FOR ASSESSING WHETHER THERE IS REASONABLE EVIDENCE OF A CAUSAL ASSOCIATION BETWEEN TAXOTERE AND IRREVERSIBLE ALOPECIA

¹⁰⁴ See Martin M. (2018). Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling. *Breast Cancer Research and Treatment* 171:627-634; Thorp N. (2014). Abstract P5-17-04: Long term hair loss in patients with early breast cancer receiving docetaxel chemotherapy. Presented at the Annual San Antonio Breast Cancer Symposium, December 9-13, 2014 ("The retrospective questionnaire study confirms that long term significant scalp alopecia (here lasting for up to 3.5 years following completion of chemotherapy) may affect 10-15% of patients following docetaxel for EBC [early breast cancer] (taking into consideration of a potential bias for no hair loss in the non-responders). This rate is higher than previous estimates. Long term hair loss to other parts of the body was also widely reported."); Bourgeois H. (2014). ERALOP study: Hair regrowth after adjuvant FEC-docetaxel chemotherapy for early breast cancer in the real life. *Journal of Clinical Oncology* Vol. 32, No.15_suppl:e12014 (reporting global persisting alopecia incidence of 33.4% at time of inquiry with median follow up period of 3.7 years); Sedlacek SW, Persistent Significant Alopecia (PSA) form Adjuvant Docetaxel after Doxorubicin/Cyclophosphamide (AC) Chemotherapy in Women With Breast Cancer. Presented at the Annual San Antonio Breast Cancer Symposium, December 14-17, 2006.

¹⁰⁵ See TAX 316 Interim Clinical Study Report, Jan. 21, 2004 (Sanofi_02640580); TAX 301/GEICAM 9805 Interim Clinical Study Report, Jan. 30, 2004 (Sanofi_00799397); TAX 316 Clinical Study Report, Sept. 9, 2010 (Sanofi_02645200); TAX 301/GEICAM 9805 Clinical Study Report, Nov. 9, 2009 (Sanofi_00799597); *see also* Docetaxel Labeling Queries from PMDA (Inquiry 160415-001), May 24, 2016 (Sanofi_01331114).

¹⁰⁶ See DOCETAXEL-Permanent/Irreversible Alopecia Presentation at meeting dated October 26, 2015, presented by Nanae Hangai and Shang Jen (Sanofi_01827600); e-mail from Emanuel Palatinsky to Ana-Carolina Giuseppi dated March 16, 2010 (Sanofi_05252079); Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788); *see generally* Summary of Product Characteristics ("*Skin and subcutaneous tissue disorders*: In study TAX 316, alopecia persisting into the follow-up period after the end of chemotherapy was reported in 687 of 744 TAC patients and 645 of 736 FAC patients. At the end of the follow-up period (actual median follow-up time of 96 months), alopecia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%). In GEICAM 9805 study, alopecia persisted into the follow-up period (median follow-up time of 10 years and 5 months) and was observed to be ongoing in 49 patients (9.2 %) in TAC arm and 35 patients (6.7 %) in FAC arm. Alopecia related to study drug started or worsened during the follow-up period in 42 patients (7.9 %) in TAC arm and 30 patients (5.8 %) in FAC arm.").

98. In my report, I have analyzed the available data in a manner consistent with the FDA’s “Guidance for Industry on Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products —Content and Format” from 2011, which provides guidance to drug manufacturers on “how to decide which adverse reactions or other potential safety hazards are significant enough to warrant inclusion in the WARNINGS AND PRECAUTIONS section.”¹⁰⁷

99. The Guidance notes, in keeping with the FDA regulations set forth above, that “[t]he WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.”¹⁰⁸

100. The FDA Guidance provides the following factors to be considered in assessing whether there is reasonable evidence of a causal association:

1. The frequency of reporting;
2. Whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active control group in controlled trials;
3. Evidence of a dose-response relationship;
4. The extent to which the adverse event is consistent with the pharmacology of the drug;

¹⁰⁷ FDA 2011 Guidance for Industry.

¹⁰⁸ *Id.* at 3. *See also* European Medicines Agency GVP Module IX: Signal Management, SME Workshop “Focus on Pharmacovigilance,” April 19, 2012 (“Signal validation: A signal becomes validated, if the verificatory process of all relevant documentation is suggestive of a new causal association, or a new aspect of a known association, and therefore justifies further assessment.”).

5. The temporal association between drug administration and the event;
6. Existence of dechallenge and rechallenge experience; and
7. Whether the adverse event is known to be caused by related drugs.¹⁰⁹

101. The use of the seven factors above in regulatory science and pharmacovigilance dates back to well before 2011. FDA as well as Sanofi employed many of these factors in earlier years to assess the causal association between an adverse event and a drug.

101.1. In 2006, the FDA's Guidance for Industry on "Adverse Reactions Section for Labeling for Human Prescription Drug and Biological Products" stated that adverse events should be listed in the adverse reactions section of a drug label where there is "some basis to believe there is a causal relationship between occurrence of an adverse event and the use of a drug," citing to C.F.R. § 201.57(c)(7).¹¹⁰ FDA noted that "decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on such factors as" the following, which are the same as those in the 2011 Labeling Guidance:

(1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) the extent of dose response, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the timing of the event relative to the time of drug exposure, (6) existence of challenge and dechallenge experience, and (7) whether the adverse event is known to be caused by related drugs."¹¹¹

101.2. FDA's 2005 FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment provided the following factors "that may suggest a causal relationship between the use of a product and the adverse event:"

¹⁰⁹ FDA 2011 Guidance for Industry.

¹¹⁰ FDA Guidance for Industry: Adverse Reactions Section for Labeling for Human Prescription Drug and Biological Products – Content and Format p. 8 (Jan. 2006).

¹¹¹ *Id.*

(1) occurrence of the adverse event in the expect time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy); (2) absence of symptoms related to the event prior to exposure; (3) evidence of positive dechallenge or positive rechallenge; (4) consistency of the event with the established pharmacological/toxicological effects of the product . . .; (5) consistency of the event with the known effects of other products in the class; (6) existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and (7) absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).¹¹²

101.3. FDA’s 2005 Reviewer Guidance on “Conducting a Clinical Safety review of a New Product Application and Preparing a Report on the Review” contained a section on “Causality Determination,” which stated:

In assessing the critical question of whether an adverse event is caused by a drug, whether the drug is capable of causing that adverse event in the population is usually of greater interest than whether the drug caused the event in each patient who reported the event, but the approach to causality is distinctly different for relatively common events and relatively rare, serious events.¹¹³

101.4. In its 2005 Reviewer Guidance, FDA directed reviewers to consider the following: (1) Was the patient in fact exposed to drug and did the adverse event occur after drug exposure?; (2) Did the patient have a clinical experience that meets the criteria for the adverse event of interest; (3) Is there a reasonably compelling alternative explanation for the event?; (4) The observed rate of occurrence of the event in the database compared to an estimated background rate; (5) Is the adverse event of a type commonly associated with drug exposure?; (6) Whether the drug is a member of a class of drugs known to be causally associated with the

¹¹² FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment p. 6-7 (Mar. 2005) (guidance for identifying and describing safety signals and, specifically, assessing case reports).

¹¹³ FDA Reviewer Guidance: Conducting a Clinical Safety review of a New Product Application and Preparing a Report on the Review p. 50-51 (Feb. 2005).

event of interest; (7) Presence of other adverse events in the database that may be associated with the event of interest; and (8) Positive re-challenge with the drug.¹¹⁴

101.5. In 2000, the FDA Draft Guidance for Industry on the “Content and Format of the Adverse Events Section of Labeling for Human Prescription Drugs and Biologics” directed reviewers and sponsors to consider the following factors in selecting events for inclusion in the adverse reactions section: “frequency of reporting, whether the adverse reaction rate for drug exceeds the placebo rate, extent of dose-response, extent to which the adverse reaction is consistent with the pharmacology of the drug, timing of the reaction relative to time of drug exposure, and whether the adverse reaction is known to be caused by related drugs.”¹¹⁵

101.6. As early as 1992, FDA defined “causality assessment” in its “Guideline for Postmarketing Reporting of Adverse Event Experiences” as the “[d]etermination of whether there is a reasonable possibility that the product is etiologically related to the adverse experience. Causality assessment includes, for example, assessment of temporal relationships, dechallenge/rechallenge information, association with (or lack of association with) underlying disease, presence (or absence) of a more likely cause, plausibility, etc.”¹¹⁶ These same factors were restated in the definition of “causality assessment” in FDA’s 2001 Draft Guidance for Industry for the Postmarketing Safety Reporting for Human Drug & Biological Products Including vaccines.¹¹⁷

¹¹⁴ See *id.* at 50-51.

¹¹⁵ FDA Draft Guidance for Industry: Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics (2000), available at <https://www.fda.gov/OHRMS/DOCKETS/98fr/001306gl.pdf>.

¹¹⁶ FDA Guidance for Industry: Postmarketing Safety Reporting for Human Drug & Biological Products Including Vaccines p. 18 (1992) (directing adverse events to be reported if there a “reasonable possibility” that the event is causally related to the drug exposure).

¹¹⁷ FDA Draft Guidance for Industry for the Postmarketing Safety Reporting for Human Drug & Biological Products Including Vaccines p. 35 (Mar. 2001).

102. Similarly, Sanofi's Pharmacovigilance Department and Standard Operating Procedures acknowledged the use of many of these factors to internally analyze a reasonable causal relationship and otherwise identify safety signals.

102.1. Sanofi's March 13, 2013 presentation on Safety Signal Detection Management in GPE provided that "Signal Evaluation" should include assessment of "Qualitative assessment: case analysis, de-challenge/re-challenge, medical plausibility; Quantitative assessment: epidemiology, claims data, registry" and further discusses case review, data mining, clinical trial review and literature surveillance as part of Sanofi's "Signal Detection Process."¹¹⁸

102.2. An April 2016 Sanofi presentation titled "Product Safety topics" discusses "signal source and context of evaluation" and its impact on "relevant current labeling" and "scientific adjudication required," and noting Sanofi's policy to analyze biologic plausibility, case reports, clinical trial data, and medical literature, amongst other items, in evaluating the existence of a reasonable causal association."¹¹⁹

103. The epidemiological literature has utilized many of these factors in assessing the relationship between a drug and an adverse event for decades also. In his seminal 1965 article "The Environment and Disease: Association or Causation?" Sir Austin Bradford Hill laid out nine "aspects of [an] association" to consider in determining whether the association is causal,

¹¹⁸ Safety Signal Detection Management in GPE, Emanuel Palatinsky, March 13, 2013 (Sanofi_1363709).

¹¹⁹ Sanofi April 2016 Presentation "Product-Safety topic" (Sanofi_01329596); *see also* Sanofi Standard Operating Procedure Supporting GPE Signal Detection for Registered Products in US Pharmacovigilance, Aug. 4, 2015 (Sanofi_PJ_00017228); Sanofi Standard Operating Procedure for Collecting, Processing and Regulatory Reporting of Solicited Adverse Events, Jan. 16, 2011 (Sanofi_PJ_0016214); Sanofi Standard Operating Procedure for Safety Signal and Risk Management, Nov. 2, 2014 (Sanofi_05061309); Sanofi Standard Operating Procedure for Safety Signal and Risk Management, Aug. 30, 2015 (Sanofi_05061269); Safety Economic Part II, Emanuel Palatinsky, Nov. 2, 2011 (Sanofi_03073713); Appendix 8: Methods of Signal Detection and Screened Sources (Sanofi_01076720).

now often referred to in pharmacoepidemiology as the Bradford Hill factors or criteria.¹²⁰ The Bradford Hill criteria include: consistency (reproducibility), temporality (whether condition followed exposure); biological gradient (dose response relationship); plausibility (whether the association is biologically plausible); experiment (whether the condition improves upon removal of the hypothesized causative agent); and analogy.¹²¹

104. As with any set of factors, FDA's set of seven factors has certain limitations. FDA does not explicitly define all the terms it uses in the factors, but there is a generally-accepted basis for the terminology in regulatory science and pharmacovigilance, and I draw upon my expertise in same in understanding and applying the factors.

105. In addition, there are certain factors that may be useful under certain circumstances but not others. For example, if there is no available dechallenge/rechallenge information or data, then it is not possible to use this factor. In addition, the factors do not include other kinds of epidemiological studies beyond controlled trials, in part because such studies are often not available.

106. I analyzed the available data in this case in light of each of these seven factors with these limitations in mind.

107. In my opinion, there is recognition on the part of FDA and the scientific and epidemiological community that not all of these factors must be present in order for there to be

¹²⁰ Hill, Austin Bradford (1965). "The Environment and Disease: Association or Causation?" Proceedings of the Royal Society of Medicine. 58(5): 295-300. PMC 1898525.

¹²¹ The complete list of the nine Hill factors is as follows: (1) strength of the association; (2) consistency (whether the association has been repeatedly observed "by different persons, in different places, circumstances and times"); (3) specificity (whether there are alternative causes of a condition); (4) temporality (whether the condition followed the exposure to the agent); (5) biological gradient (whether a dose-response relationship exists); (6) plausibility (whether the association is biologically plausible); (7) coherence (whether the association "seriously conflict[s] with the generally known facts of the natural history and biology of the disease"); (8) experiment (whether the condition improves upon removal of the hypothesized causative agent); and (9) analogy. *See id.*

reasonable evidence of a causal association such that a Warning is warranted. In fact, FDA’s language in the Guidance says that “some factors to consider”¹²²

108. Moreover, as the Guidance notes,¹²³ the FDA Warning Standard states that “a causal relationship need not have been definitively established.”¹²⁴ The question to be addressed is thus whether a substantial majority of the factors that can be assessed demonstrate reasonable evidence of a causal association.

109. In a review and analysis performed by Sanofi in 2015 (hereinafter referred to as “Sanofi’s 2015 Causation Analysis”), Sanofi concluded in its internal and regulatory communications that “Based on review of the Sanofi global pharmacovigilance database, worldwide scientific literature, clinical studies, and biological plausibility, the cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.”¹²⁵ I agree with Sanofi’s conclusion that there was reasonable evidence of a causal association between Taxotere and irreversible alopecia. As discussed below, based on many of the same factors analyzed by Sanofi,¹²⁶ I conclude that such evidence existed by as early as 2009.

¹²² FDA Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products (2011) at 3, available at <https://www.fda.gov/downloads/drugs/guidances/ucm075096.pdf>.

¹²³ *Id.*

¹²⁴ 71 Fed. Reg. 3922-3997 (January 24, 2006) at 3990.

¹²⁵ European Medicines Agency, CHMP Type II Variation Assessment Report, May 12, 2016; Sanofi LRC Topic: Docetaxel CCDS v 30, Permanent/irreversible alopecia, Vanina Groult, Global Regulatory Affairs Labeling (GRAL), Nov. 16, 2015 (Sanofi_01101022); Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788); Sanofi Safety Management Committee Meeting Minutes, Oct. 26, 2015 (Sanofi_01827599); *see also* Email from Nanae Hangai to Yoshiko Shimazaki and Vanina Groult, Feb. 16, 2016 (Sanofi_02664951) (“The bottom line is: **cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.**”) (emphasis in original).

¹²⁶ Although Sanofi was communicating its conclusion regarding a causal association between Taxotere and irreversible alopecia in 2015 (as set forth in the documents cited in the above footnote), the data and information both relied upon by Sanofi to reach this conclusion and otherwise available to Sanofi dates back far earlier, as

VIII. APPLICATION OF FACTORS FROM FDA LABELING GUIDANCE TO THE DATA REGARDING TAXOTERE AND IRREVERSIBLE ALOPECIA

A. First Factor: The Frequency of Reporting

110. For the frequency of reporting factor, I reviewed when safety signals emerged in FDA’s Adverse Event Reporting System (FAERS) for Taxotere and adverse events associated with irreversible alopecia.

111. The emergence of a safety signal for a particular drug and event does not in itself establish that the association is causal, but generates a hypothesis that warrants additional investigation. As FDA has stated, “Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.”¹²⁷

112. FAERS data has recognized limitations that arise from its nature as a voluntary reporting system, including underreporting and stimulated reporting, and event reports with incomplete information.¹²⁸ Nonetheless, it has played an important role in regulatory review of drug safety issues, and in decisions regarding labeling changes.¹²⁹

discussed more fully in my analysis below. *See also* Email from Emanuel Palatinsky to Nanae Hangai, Jan. 22, 2014 (Sanofi_01718843) (“It is up to the GSO to determine with certainty the ADRs that have an important impact on public health, as you have correctly identified from the regulatory guideline. Especially in relation to well characterized safety signals (*e.g.*, persistent alopecia . . .”).

¹²⁷ FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment p. 4, 9 (Mar. 2005).

¹²⁸ *Id.* at 9.

¹²⁹ See, e.g., Lester, J., Neyarapally, G. A., Lipowski, E., Graham, C. F., Hall, M., & Dal Pan, G. (2013). Evaluation of FDA safety-related drug label changes in 2010. *Pharmacoepidemiology and Drug Safety*, 22(3), 302-305. Moore, T. J., Singh, S., & Furberg, C. D. (2012). The FDA and new safety warnings. *Archives of Internal Medicine*, 172(1), 78-80.

113. While I am a Professor of Biostatistics, as has been my practice both as FDA Commissioner and in my academic appointments, and as is standard for regulatory experts, I utilize the work of biostatisticians where appropriate.

114. I requested that biostatistician David Madigan, Ph.D., Professor of Statistics at Columbia University, calculate when a safety signal emerged in FAERS for endpoints related to irreversible alopecia. Dr. Madigan searched MedWatch Reports from 2000 through 2017 with Higher Level Term (“HLT”) alopecia and tagged with an outcome of “Disability or Permanent Damage.”¹³⁰ The search terms are listed in Dr. Madigan’s liability report.¹³¹

115. Dr. Madigan calculated when a safety signal emerged for these endpoints using certain recognized signaling statistics including the Proportional Reporting Ratio (“PRR”), Empirical Bayes Geometric Mean (“EBGM”), and EB05.¹³² I use the results of those calculations as stated in his expert report of November 2, 2018.

116. The PRR is a widely-recognized measure in signal detection for drug-associated adverse events, including by FDA,¹³³ and Sanofi’s pharmacovigilance department cited use of this measure as part of safety signal detection management.¹³⁴

117. As set forth in the Evans article cited by FDA, a PRR signal exists where the PRR is ≥ 2 , there are at least 3 cases, and chi-squared is ≥ 4 .¹³⁵

¹³⁰ Madigan Report of November 2, 2018 at 11-16 (“Madigan Report”).

¹³¹ *Id.*

¹³² Dr. Madigan also performed a lasso logistic regression analysis to assess the impact of the innocent bystander effect. *Id.* at 15-16.

¹³³ Evans SJ, Waller PC, Davis S. (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf*, 10(6), 483-486; Finney DJ (1974). Systemic signaling of adverse reactions to drugs. *Methods Inf Med*. 13(1):1-10; Heshia J. Data Mining at FDA (“The Proportional Reporting Ratio (PRR) is the foundational concept for many disproportionality methods.”); Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005.

¹³⁴ Safety Signal Detection Management in GPE, Emanuel Palatinsky, March 13, 2013 (Sanofi_1363709).

118. Dr. Madigan’s calculations of this signal detection measure for the drug-adverse event pair of Taxotere and HLT alopecia with “Disability or Permanent Damage” yielded a signal date beginning in the First Quarter of 2000, and continuing without interruption through the end of his analysis in the Fourth Quarter of 2017.¹³⁶

119. I also reviewed and analyzed reports disclosed to Sanofi in Sanofi’s internal global pharmacovigilance database, data from Sanofi’s own clinical trial studies, reports in the medical literature, and inquiries and correspondence about this injury from patients, physicians, and foreign regulatory authorities.

120. At my request, Dr. Madigan performed a review of Sanofi’s internal global pharmacovigilance database. Dr. Madigan identified 291 cases of irreversible alopecia in Sanofi’s internal global pharmacovigilance database from 1999 through 2015.¹³⁷

121. In Sanofi’s 2015 Causation Analysis, Sanofi performed a review of its internal global pharmacovigilance database. Sanofi identified 117 cases reporting irreversible alopecia based on its methodology,¹³⁸ which was limited to “a verbatim event that included either ‘permanent’ or ‘irreversible’, or alopecia that lasted more than 2 years with an outcome of not recovered/recovering/unknown.”¹³⁹ This represented 5.3% of the 2,172 cases reporting a HLT

¹³⁵ Evans SJ, Waller PC, Davis S. (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf*, 10(6), 483-486; *see* Hessa J. Data Mining at FDA (“The Proportional Reporting Ratio (PRR) is the foundational concept for many disproportionality methods.”); Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005.

¹³⁶ Madigan Report at 11-16. Dr. Madigan also found a signal date using EBGM in 2008, using EB05 in 2012, and using lasso logistic regression analysis in 2010. *Id.*

¹³⁷ Madigan Report at 16-18. When narrowed to exclude any cases labeled as “recovered” in the database, Dr. Madigan identified 263 cases of irreversible alopecia. *Id.*

¹³⁸ As noted by Sanofi, “there are obvious finding that the docetaxel has been involving in these case; some cases only reported docetaxel as suspect drugs. And combinations are mostly AC/EC, but random.” Email from Nanae Hangai, Jan. 22, 2016 (Sanofi_02664951).

¹³⁹ *See* Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788).

“Alopecia.”¹⁴⁰ Sanofi’s definition of irreversible alopecia does not conform to the definition of irreversible alopecia generally set forth in the medical literature,¹⁴¹ and Sanofi recognized internally that if the two-year time period was reduced, there would be “more cases.”¹⁴²

122. Sanofi’s 2015 Causation Analysis cited to the reports it identified in its internal global pharmacovigilance database to support its conclusion that “the cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.”¹⁴³

123. Sanofi’s internal clinical trial studies identified reports of irreversible alopecia following Taxotere treatment. The 2004 interim data and 2009 final data from two of Sanofi’s clinical trials (TAX 316 and TAX 301/GEICAM 9805) identified an incidence rate or rate of occurrence ranging from 3.2% - 9.2%.¹⁴⁴ Sanofi’s 2015 Causation Analysis cited to these

¹⁴⁰ *Id.*

¹⁴¹ See Section V. of this Report (citing to medical literature defining condition as “complete loss of growth or partial regrowth at least 6 months after chemotherapy.”). Sanofi previously performed a review of its global pharmacovigilance database in 2011. See Sanofi, 2.5 Clinical Overview Docetaxel - Persistent Alopecia, January 18, 2011 (Sanofi_04353204). In its 2011 review, Sanofi identified 1,620 cases with HLT “Alopecia” but defined the injury to be “not recovered \geq 12 months following the last dose of chemotherapy.” *Id.* Although the time period in its 2011 analysis was \geq 12 months rather than 24 months, this definition also fails to conform to the definition of irreversible alopecia generally set forth in the medical literature as described in Section V. of this Report. This definition resulted in 142 identified cases (8.8%) of those reporting HLT “Alopecia.” *Id.*

¹⁴² Email from Nanae Hangai to Yoshiko Shimazaki and Vanina Groult, Feb. 16, 2016 (Sanofi_02664951) (“Therefore, I selected the cases: 1. If the verbatim contains ‘permanent’ or ‘irreversible’ and 2. The verbatim does not contains ‘permanent’ or ‘irreversible’ but lasted more than 2 years (**since if set less, we know we have more cases.**)” (emphasis added)).

¹⁴³ European Medicines Agency, CHMP Type II Variation Assessment Report, May 12, 2016; Sanofi LRC Topic: Docetaxel CCDS v 30, Permanent/irreversible alopecia, Vanina Groult, Global Regulatory Affairs Labeling (GRAL), Nov. 16, 2015 (Sanofi_01101022); Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788); Sanofi Safety Management Committee Meeting Minutes, Oct. 26, 2015 (Sanofi_01827599). Although Sanofi identified more reports in 2011 (142) than it did using the longer 24-month timeframe in 2015 (117), Sanofi concluded in its 2011 review that these reports “revealed no evidence of a causal relationship with docetaxel” Sanofi, 2.5 Clinical Overview Docetaxel - Persistent Alopecia, January 18, 2011 (Sanofi_04353204).

¹⁴⁴ See TAX 316 Interim Clinical Study Report, Jan. 21, 2004 (Sanofi_02640580); TAX 301/GEICAM 9805 Interim Clinical Study Report, Jan. 30, 2004 (Sanofi_00799397); TAX 316 Clinical Study Report, Sept. 9, 2010 (Sanofi_02645200); TAX 301/GEICAM 9805 Clinical Study Report, Nov. 9, 2009 (Sanofi_00799597); see also Docetaxel Labeling Queries from PMDA (Inquiry 160415-001), May 24, 2016 (Sanofi_01331114).

clinical trial studies and the reports of irreversible alopecia reported to support its conclusion that “the cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.”¹⁴⁵

124. The publically available medical literature disclosed reports of irreversible alopecia associated with Taxotere.¹⁴⁶ Sanofi’s 2015 Causation Analysis¹⁴⁷ cited to certain of this

¹⁴⁵ European Medicines Agency, CHMP Type II Variation Assessment Report, May 12, 2016; Sanofi LRC Topic: Docetaxel CCDS v 30, Permanent/irreversible alopecia, Vanina Groult, Global Regulatory Affairs Labeling (GRAL), Nov. 16, 2015 (Sanofi_01101022); Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788); Sanofi Safety Management Committee Meeting Minutes, Oct. 26, 2015 (Sanofi_01827599).

¹⁴⁶ See, e.g., Kang D. (2018). Permanent Chemotherapy-Induced Alopecia in Patients with Breast Cancer: A 3-Year Prospective Cohort Study. *The Oncologist* 23:1-7 (describing women being administered docetaxel as part of a taxane-based regimen versus other regimens and finding that “[p]atients with taxane-based treatment had about eight times higher odds of PCIA [permanent chemotherapy-induced alopecia] 3 years after completion of chemotherapy (8.01; 95% CI, 1.20-53.26] adjusting for age, hair density, and thickness at diagnosis.”); Martin M. (2018). Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling. *Breast Cancer Research and Treatment* 171:627-634; Crown J. (2017). Incidence of permanent alopecia following adjuvant chemotherapy in women with early stage breast cancer. *J Clin Oncol*, available at http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e21576; Fonia A. (2017). Permanent alopecia in patients with breast cancer after taxane chemotherapy and adjuvant hormonal therapy: Clinicopathologic findings in a cohort of 10 patients. *J Am Acad Dermatol*, available at <http://dx.doi.org/10.1016/j.jaad.2016.12.027>; Namini S. (2016). Systematic Review of the Risk of Permanent Alopecia with Docetaxel Treatment for Breast Cancer. *J Clin Case Rep* 6:851; Sibaud V. (2016). Dermatological adverse events with taxane chemotherapy. *Eur J. Dermatol* 26(5): 427-443; Bourgeois H. (2014). ERALOP study: Hair regrowth after adjuvant FEC-docetaxel chemotherapy for early breast cancer in the real life. *Journal of Clinical Oncology* Vol. 32, No.15_suppl:e12014; Thorp N. (2014). Abstract P5-17-04: Long term hair loss in patients with early breast cancer receiving docetaxel chemotherapy. Presented at the Annual San Antonio Breast Cancer Symposium, December 9-13, 2014; Tosti A. (2013). Docetaxel and permanent alopecia. *J Am Acad Dermatol*, available at <http://dx.doi.org/10.1016/j.jaad.2010.06.064>; Kluger N. (2012). Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients. *Ann Oncol* 23(11):2879-84; Miteva M. (2011). A Permanent alopecia after systemic chemotherapy: a clinicopathological study of 10 cases. *Am J Dermatopathol* 33(4):345-50; Palamaras I. (2011). Permanent chemotherapy-induced alopecia: A review. *J Am Acad Dermatol* 64(3):604-606; Tallon B. (2010). Permanent chemotherapy-induced alopecia: case report and review of the literature. *J Am Acad Dermatol* 63(2):333-336; Burgeois H. (2009). Long term persistent alopecia and suboptimal hair regrowth after adjuvant chemotherapy for breast cancer: Alert for an emerging side effect: ALOPERS Observatory, *Cancer Research* 69(24 Suppl): Abstract nr 3174; Prevezas C. (2009). Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *Br J Dermatol* 160(4):883-885; Sedlacek SW, Persistent Significant Alopecia (PSA) form Adjuvant Docetaxel after Doxorubicin/Cyclophosphamide (AC) Chemotherapy in Women With Breast Cancer. Presented at the Annual San Antonio Breast Cancer Symposium, December 14-17, 2006; Park J. (2005). Five cases of permanent alopecia following chemotherapy. *Korean J Dermatol* 43:1365-70; see also SABCS Interview Series, May 14, 2010, available at https://www.onclive.com/publications/obtn/2010/march2010/sabcs_interview_series (“How many patients out of the 82 reports you looked at suffered permanent hair loss? One hundred percent, and now [there] are 100 women! Dramatic!”). See also Schedule 5, Studies Regarding the Risk of Irreversible Alopecia Associated with Taxotere and Details of Other Studies Cited or Referenced in This Report; see also Email from Madeline Malia to Mark Gaydos, March 16, 2010 (Sanofi_05446831, Gaydos Ex. 26) (internally forwarding abstract of Burgeois H. (2009). Long term persistent alopecia and suboptimal hair regrowth after adjuvant chemotherapy for breast cancer:

medical literature in supporting its conclusion that “the cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.”¹⁴⁸

125. Sanofi also received inquiries and correspondence regarding reports of irreversible alopecia from patients, physicians, internal Sanofi departments, and foreign regulatory authorities.¹⁴⁹

126. In my opinion, the frequency of reporting from the sources discussed above beginning as early as 2009 reveals safety signals that were evident and warranted further investigation, including consideration of the other factors set forth in this Report.

B. Second Factor: Whether the Adverse Event Rate in the Drug Treatment Group Exceeds the Rate in the Placebo and Active Control Group in Controlled Trials

Alert for an emerging side effect: ALOPERS Observatory, Cancer Research 69(24 Suppl): Abstract nr 3174 to Vice President of general medicine US advertising and promotion in North American global regulatory affairs Mark Gaydos); Emails between Gina Vestea and Mark Gaydos, August 21, 2012 (Sanofi_04691718, Gaydos Ex. 28) (internally forwarding Kluger (2012) and Miteva (2011) abstracts).

¹⁴⁷ Sanofi’s 2011 review cited to other medical literature. *See* Sanofi, 2.5 Clinical Overview Docetaxel - Persistent Alopecia, January 18, 2011 (Sanofi_04353204) (citing Prevezas C. (2009). Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *Br J Dermatol* 160(4):883-885; Tallon B. (2010). Permanent chemotherapy-induced alopecia: case report and review of the literature. *J Am Acad Dermatol* 63(2):333-336; Roche H. (2006). Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. *J Clin Oncol* 24(36):56664-5671).

¹⁴⁸ European Medicines Agency, CHMP Type II Variation Assessment Report, May 12, 2016; Sanofi LRC Topic: Docetaxel CCDS v 30, Permanent/irreversible alopecia, Vanina Groult, Global Regulatory Affairs Labeling (GRAL), Nov. 16, 2015 (Sanofi_01101022); Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788) (citing Kluger N. (2012). Permanent scalp alopecia related to breast cancer chemotherapy by sequential fluorouracil/epirubicin/cyclophosphamide (FEC) and docetaxel: a prospective study of 20 patients. *Ann Oncol* 23(11):2879-84; Miteva M. (2011). A Permanent alopecia after systemic chemotherapy: a clinicopathological study of 10 cases. *Am J Dermatopathol* 33(4):345-50); Sanofi Safety Management Committee Meeting Minutes, Oct. 26, 2015 (Sanofi_01827599).

¹⁴⁹ *See, e.g.*, Gaydos Exhibit 23 (Sanofi_05446835); Vestea Exhibit 8 (Sanofi_04731188); Email from Lynette Melman, Dec. 4, 2012 (Sanofi_01363974); Gaydos Exhibit 24 (Sanofi_05075741); AFSSAPS letter, July 9, 2010 (Sanofi_03643994); Emails from Heidi Filternborg, Mar. 3-8, 2006 (Sanofi_01035453; Sanofi_01035459); Response to EMA Agency Request, Sept. 22, 2011 (Sanofi_01112867).

127. For this factor I considered if and when there was evidence that the adverse event rate for irreversible alopecia in Taxotere subjects exceeded the rate in comparator groups in controlled trials.

128. In 1999, Sanofi commenced two clinical trial studies (TAX 316 and TAX 301/GEICAM 9805), both of which sought to compare patients receiving docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus those receiving 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC).¹⁵⁰ Sanofi prepared interim clinical study reports for both trials in 2004, and final clinical study reports for both trials in 2009.¹⁵¹ The interim and final clinical study reports for both clinical trials provided data and information regarding irreversible alopecia in patients in the TAC and FAC arms.¹⁵²

129. At my request, Dr. Madigan performed a statistical analysis comparing the adverse event rate for irreversible alopecia in the TAC versus FAC arms from the TAX 316 and TAX 301/GEICAM 9805 clinical trials.¹⁵³ Dr. Madigan's analysis demonstrates a statistically significant increased risk of irreversible alopecia for patients in the TAC arm versus the FAC arm at nearly all time periods in both the TAX 316 TAX 301/GEICAM 9805 clinical trials.¹⁵⁴ I

¹⁵⁰ TAX 316 Interim Clinical Study Report, Jan. 21, 2004 (Sanofi_02640580); TAX 301/GEICAM 9805 Interim Clinical Study Report, Jan. 30, 2004 (Sanofi_00799397); TAX 316 Clinical Study Report, Sept. 9, 2010 (Sanofi_02645200); TAX 301/GEICAM 9805 Clinical Study Report, Nov. 9, 2009 (Sanofi_00799597).

¹⁵¹ *Id.*

¹⁵² *Id.*

¹⁵³ Madigan Report at 18-20.

¹⁵⁴ The risk ratio of irreversible alopecia for patients in the TAC arm versus the FAC at the 2009 final time period for the TAX 316 clinical trial is 1.80, 95% confidence interval (0.98, 3.28). *Id.* Nevertheless, based on my review and Dr. Madigan's report, the incidence rate for irreversible alopecia in both GEICAM 9805/TAX 301 and TAX 316 may be under reported. *See id.*

The number of subjects followed into the follow-up period for GEICAM 9805/TAX 301 was only 49/532 (9.2%). *See* TAX 301/GEICAM 9805 Interim Clinical Study Report, Jan. 30, 2004 (Sanofi_00799397); TAX 301/GEICAM 9805 Clinical Study Report, Nov. 9, 2009 (Sanofi_00799597). As Sanofi acknowledges, the final clinical trial report for GEICAM 9805/TAX 301 states "during 5 year follow-up, the CSR [clinical trial report] notes 'Most TEAEs were followed into the follow-up period at the discretion of the Investigator.' This implies that the most of cases of alopecia were not followed during the follow up period in the GEICAM study." Nanae Hangai, Docetaxel

have seen no evidence that Sanofi conducted any statistical analysis comparing the risk of irreversible alopecia in the TAC versus FAC arms of either the TAX 316 or TAX 301/GEICAM 9805 clinical trials at any other time.¹⁵⁵

130. At my request, Dr. Madigan also conducted a pooled analysis of the adverse event rates for irreversible alopecia from the TAX 316 and TAX 301/GEICAM 9805 clinical trials.¹⁵⁶ I have seen no evidence that Sanofi conducted such a pooled analysis at any time.

131. Dr. Madigan's random effects meta-analysis demonstrates that, when the data from the TAX 316 and TAX 301/GEICAM 9805 clinical trials is pooled, there is a statistically significant increased risk of irreversible alopecia for patients in the TAC arm versus the FAC arm (a rate ratio of 1.85 with a corresponding 95% confidence interval (1.04, 3.31) and a p-value of 0.04).¹⁵⁷

132. Sanofi's 2015 Causation Analysis cited to these clinical trial studies and the adverse event rates of irreversible alopecia reported to support its conclusion that "the

Labeling Queries from PMDA [Japan's Pharmaceutical and Medical Devices Agency], May 24, 2016 (Sanofi_01331114).

For TAX 316, Sanofi acknowledges that its follow-up reporting and collection strategy did not include capturing adverse event start and stop dates to fully understand the duration of adverse events like irreversible alopecia. *See, e.g.*, Email from Jean-Philippe Aussel to Catherine Crane and Michael Kopreski, May 21, 2012 (Sanofi_02932469) ("I confirm also that the CRF AE modules did not capture AE start and stop dates Note for very large adjuvant trials conducted on product with a well known safety profile (here Taxotere) and in which AE durations are not analyzed, the collection of AE start and stop dates would have yielded only extra validation, queries etc for no added value in terms of safety results. FYI-similar AE collection strategy (without dates) was applied for the TAX-316/BCIRG-001 early breast cancer pivotal registration study without any consequences on the positive outcomes of the FDA/EMA approvals.").

¹⁵⁵ *See also* Deposition of Barry Childs, M.D., October 26, 2018 at 113:23-114:9 ("Q. Do you know whether Sanofi ever engaged in any clinical trials to determine whether or not Taxotere can cause permanent hair loss in some people who are administered the drug? A. I'm not aware that Sanofi did that, and I certainly was not part of anything that they did with respect to that.") (objection omitted).

¹⁵⁶ Madigan Report at 18-20.

¹⁵⁷ *Id.*

cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.”¹⁵⁸

133. In my opinion, there was evidence that the adverse event rate for irreversible alopecia in Taxotere subjects exceeded the rate in comparator groups in controlled in as early as 2009.

C. Third Factor: Whether There Is Evidence of a Dose-Response Relationship

134. For this factor I considered whether there is evidence of a dose-response relationship between Taxotere and adverse events of irreversible alopecia.

135. In a 2018 study by Martin titled “Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling,” the authors evaluated, among other things, the prevalence of irreversible alopecia following adjuvant docetaxel for breast cancer, patients receiving Taxotere regimens at a cumulative dose equal to or greater than 400 mmg/m² had a significantly higher incidence of irreversible alopecia.¹⁵⁹

136. In addition, in the 2018 Martin study, complete irreversible alopecia was seen in patients receiving docetaxel regimens with a cumulative dose of equal to or greater than 400

¹⁵⁸ European Medicines Agency, CHMP Type II Variation Assessment Report, May 12, 2016; Sanofi LRC Topic: Docetaxel CCDS v 30, Permanent/irreversible alopecia, Vanina Groult, Global Regulatory Affairs Labeling (GRAL), Nov. 16, 2015 (Sanofi_01101022); Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788); Sanofi Safety Management Committee Meeting Minutes, Oct. 26, 2015 (Sanofi_01827599).

¹⁵⁹ As compared to other chemotherapy regimens, including lower dose regimens of docetaxel, the prevalence of irreversible alopecia increased 33-52% in patients treated with docetaxel regimens having a cumulative dose equal to or exceeding 400mmg/m². *See* Martin M. (2018). Persistent Major Alopecia Following Adjuvant Docetaxel for Breast Cancer: Incidence, Characteristics, and Prevention with Scalp Cooling. *Breast Cancer Research and Treatment* 171:627-634.

mmg/m² (36/358, 10.06%, 95% CI 7.36-13.61).¹⁶⁰ In the 59 patients receiving docetaxel regimens less than 400 mmg/m², no instances of complete irreversible alopecia were reported.¹⁶¹

137. Other studies I reviewed reached similar conclusions.

137.1. For example, in a 2017 abstract authored by Crown titled “Incidence of permanent alopecia following adjuvant chemotherapy in women with early stage breast cancer,” he concluded that “For patients receiving D [Docetaxel] non A [Anthracyclines], the risk is dose-dependent.”¹⁶²

137.2. In a 2014 presentation by Bourgeois at the San Antonio Breast Cancer Symposium titled “ERALOP: Post-adjuvant FEC-docetaxel chemotherapy for early breast cancer: hair regrowth in the real life,” he found that “Docetaxel dose reduction: dose reduction (acute toxicity) is correlated with a PSA [Persisting Significant Alopecia] decrease (reversible alopecia) OR =.43 [0.30-0.89].”¹⁶³

138. I found no evidence of a study concluding that a dose-response relationship failed to exist.¹⁶⁴

139. In my opinion, based on the above, there was reproducible evidence of a dose response relationship between Taxotere and irreversible alopecia beginning as early as 2009.

D. Fourth Factor: The Extent to Which the Adverse Event Is Consistent with the Pharmacology of the Drug

¹⁶⁰ *Id.* In addition, the incidence of complete irreversible alopecia was similar in patients with (22/221, 9.96%) and without hormonal therapy (14/137, 10.2%).

¹⁶¹ *Id.*

¹⁶² Crown J. (2017). Incidence of permanent alopecia following adjuvant chemotherapy in women with early stage breast cancer. J Clin Oncol, available at http://ascopubs.org/doi/abs/10.1200/JCO.2017:35.15_suppl.e21576

¹⁶³ Bourgeois H. (2014). ERALOP: Post-adjuvant FEC-docetaxel chemotherapy for early breast cancer: hair regrowth in the real life. San Antonio Breast Cancer Symposium, Dec. 9-13, 2014 (P5-21-05)).

¹⁶⁴

140. For this factor, I reviewed, based on my own experience and knowledge, the medical literature, and Sanofi's internal documents, whether and when there was evidence that irreversible alopecia is consistent with the pharmacology of Taxotere. In other words, at what point in time, if any, was there evidence of a plausible biological mechanism by which Taxotere can cause irreversible alopecia

141. A *plausible* biological mechanism differs from a *known* biological mechanism.¹⁶⁵ Biological plausibility is satisfied if the relationship is consistent with the current body of knowledge regarding the etiology and mechanism of disease.¹⁶⁶

142. Anagen effluvium, which is the pathologic loss of hair during the anagen (first) phase of the hair's growth cycle, is a common adverse event of cytotoxic drugs, including agents like Taxotere.

143. As explained in Sanofi's 2015 Causation Analysis, "[c]ytotoxic chemotherapy agents target rapidly dividing cells and as a result the highly proliferative hair matrix cells are an unintended target."¹⁶⁷

144. As a result, anagen phase hairs are rapidly lost because of massive apoptosis of hair matrix cells of hair bulbs.¹⁶⁸

145. It is not well understood how this type of chemotherapy-induced alopecia becomes irreversible but a number of hypotheses have been put forth by Sanofi and in the medical literature.

¹⁶⁵ Weed D. (1998). Biologic Plausibility in Causal Inference: Current Method and Practice. Am J Epidemiol 147:415-25.

¹⁶⁶ Fedak K. (2015). Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol 12:14.

¹⁶⁷ Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788).

¹⁶⁸ See Bodó E. (2007). Dissecting the Impact of Chemotherapy on the Human Hair Follicle. Am J Pathology 171:1153-68.

146. In its 2015 Causation Analysis, Sanofi included a section specific to “Biologic Plausibility,” which identified the following hypotheses: “toxic damage to stem cells/hair matrix cells of the hair bulb or disturbance of the signaling pathway to the secondary hair germ.”¹⁶⁹

147. The medical literature likewise supports these hypotheses.¹⁷⁰

148. Sanofi’s 2015 Causation Analysis cited to its review of biologic plausibility in reaching its conclusion that “the cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.”¹⁷¹

149. In my opinion, there was evidence of a plausible biological mechanism by which Taxotere can cause irreversible alopecia in as early as 2009.

E. Fifth Factor: The Temporal Association Between Drug Administration and the Event

150. For this factor, I looked for adverse event reports received by Sanofi of irreversible alopecia showing that the adverse event occurred after the patient was exposed to Taxotere.

151. It is almost always the case that adverse event reports involve an adverse event that occurs after the patient is exposed to the suspect drug. While in some cases a report may

¹⁶⁹ Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788)

¹⁷⁰ See, e.g., Fonia A. (2017). Permanent alopecia in patients with breast cancer after taxane chemotherapy and adjuvant hormonal therapy: Clinicopathologic findings in a cohort of 10 patients. *J Am Acad Dermatol*, available at <http://dx.doi.org/10.1016/j.jaad.2016.12.027>; Miteva M. (2011). Permanent Alopecia After Systemic Chemotherapy: A Clinicopathological Study of 10 Cases. *Am J Dermatopathol* 33:345-350; Paus R. (2013). Pathobiology of chemotherapy-induced hair loss. *Lancet Oncol* 14: e50–59; Prevezas C. (2009). Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. *British Journal of Dermatology*; 160:881-898.

¹⁷¹ European Medicines Agency, CHMP Type II Variation Assessment Report, May 12, 2016; Sanofi LRC Topic: Docetaxel CCDS v 30, Permanent/irreversible alopecia, Vanina Groult, Global Regulatory Affairs Labeling (GRAL), Nov. 16, 2015 (Sanofi_01101022); Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788); Sanofi Safety Management Committee Meeting Minutes, Oct. 26, 2015 (Sanofi_01827599).

involve a worsening of a pre-existing condition or the reappearance of an event that also occurred earlier in the person's medical history, this would still satisfy the temporality criterion.

152. As indicated in the discussions of the frequency or reporting and controlled trials above, Sanofi received numerous adverse event reports of irreversible alopecia involving Taxotere. For example, as discussed above, Dr. Madigan identified 291 cases of irreversible alopecia in Sanofi's internal global pharmacovigilance database from 1999 through 2015.¹⁷² These events occurred after the person was exposed to Taxotere.

153. Sanofi's 2015 Causation Analysis cited to its global pharmacovigilance database with reports of irreversible alopecia after Taxotere treatment to support its conclusion that "the cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel."¹⁷³

154. In my opinion, these numbers establish this temporal association factor by as early as 2009.

F. Sixth Factor: Existence of Dechallenge and Rechallenge Experience

155. "Dechallenge" refers to the dose reduction or discontinuation of a drug from a patient's treatment. A positive dechallenge denotes the disappearance or reduction in severity of the adverse event. "Rechallenge" refers to the reintroduction or increase in dose of a drug suspected of having caused an adverse experience following a positive dechallenge. A positive rechallenge is reoccurrence of the adverse event upon reintroduction or increase in dose of the drug.

¹⁷² Madigan Report at 16-18.

¹⁷³ European Medicines Agency, CHMP Type II Variation Assessment Report, May 12, 2016; Sanofi LRC Topic: Docetaxel CCDS v 30, Permanent/irreversible alopecia, Vanina Groult, Global Regulatory Affairs Labeling (GRAL), Nov. 16, 2015 (Sanofi_01101022); Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788); Sanofi Safety Management Committee Meeting Minutes, Oct. 26, 2015 (Sanofi_01827599).

156. Based on my review of the data available for Taxotere, there is insufficient information regarding dechallenge and rechallenge experiences to render an opinion regarding the existence of this factor.

G. Seventh Factor: Whether the Adverse Event Is Known to Be Caused by Related Drugs

157. For this factor, I analyzed whether irreversible alopecia is known to be caused by related drugs. In particular, at my request, Dr. Madigan analyzed if and when safety signals emerged in FAERS for adverse events associated with irreversible alopecia and the following other related drugs: paclitaxel, fluorouracil, cyclophosphamide, doxorubicin, and cisplatin.¹⁷⁴

158. Dr. Madigan searched MedWatch Reports from 2000 through 2017 with Higher Level Term (“HLT”) alopecia and tagged with an outcome of “Disability or Permanent Damage” and analyzed whether a PRR signal existed (where the PRR is ≥ 2 , there are at least 3 cases, and chi-squared is ≥ 4).¹⁷⁵

159. Dr. Madigan’s calculations of this signal detection measure yielded a signal date:

- For paclitaxel: beginning in Second Quarter of 2001 through the First Quarter of 2004, then from the First Quarter of 2005 through the Third Quarter of 2006, then from the Fourth Quarter of 2008 through the Second Quarter of 2009, and then at no time thereafter.
- For fluorouracil: no signal
- For cyclophosphamide: no signal
- For doxorubicin: no signal

¹⁷⁴ Madigan Report at 11-16. These are other cancer medications used in adjuvant care for early stage breast cancer that have or could be competitors for Taxotere. *Id.*

¹⁷⁵ *Id.*; Evans SJ, Waller PC, Davis S. (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf*, 10(6), 483-486; *see* Hessa J. Data Mining at FDA (“The Proportional Reporting Ratio (PRR) is the foundational concept for many disproportionality methods.”); Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005.

- For cisplatin: no signal¹⁷⁶

160. Paclitaxel is the only comparator drug that yielded a PRR signal at any time, but the signal was early, smaller, and dissipates over time.¹⁷⁷ Taxotere is the only drug that yielded a PRR signal for irreversible alopecia that emerged continuously during the entire 2000 through 2017 time period Dr. Madigan analyzed, Taxotere was also the only drug to ever exhibit a safety signal using EBGM, EB05, and/or lasso logistic regression analysis at any time, and Taxotere was shown to have more cumulative reports of irreversible alopecia than all of the other comparator drugs combined.¹⁷⁸

161. I also reviewed publically available medical literature, Sanofi's clinical trial data, and documents produced by Sanofi in this litigation to determine whether irreversible alopecia is known to be caused by these other related drugs.¹⁷⁹ Based on my review, while many of these drugs are associated with alopecia, reports regarding irreversible alopecia are more prevalent with Taxotere than these other drugs.¹⁸⁰

162. I have seen no evidence that Sanofi ever communicated internally or externally that irreversible alopecia was known to be caused by any drug other than Taxotere.¹⁸¹

¹⁷⁶ Madigan Report at 11-16 Dr. Madigan also analyzed whether a signal existed for any comparator drug using EBGM, EB05 and lasso logistic regression analysis. *Id.* There was no safety signal for any comparator drug using any of these other safety signals at any time. *Id.*

¹⁷⁷ *Id.*

¹⁷⁸ *Id.*

¹⁷⁹ See, e.g., TAX 316 Interim Clinical Study Report, Jan. 21, 2004 (Sanofi_02640580); TAX 301/GEICAM 9805 Interim Clinical Study Report, Jan. 30, 2004 (Sanofi_00799397); TAX 316 Clinical Study Report, Sept. 9, 2010 (Sanofi_02645200); TAX 301/GEICAM 9805 Clinical Study Report, Nov. 9, 2009 (Sanofi_00799597); see Schedule 5, Studies Regarding the Risk of Irreversible Alopecia Associated with Taxotere and Details of Other Studies Cited or Referenced in This Report.

¹⁸⁰ *Id.*

¹⁸¹ See European Medicines Agency, CHMP Type II Variation Assessment Report, May 12, 2016; Sanofi LRC Topic: Docetaxel CCDS v 30, Permanent/irreversible alopecia, Vanina Groult, Global Regulatory Affairs Labeling (GRAL), Nov. 16, 2015 (Sanofi_01101022); Sanofi, 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788); Sanofi Safety Management Committee Meeting Minutes, Oct. 26, 2015 (Sanofi_01827599); see also E-mails between Sanofi's Michael Kopreski and Nanae Hangai, October 22, 2015

163. Based on my discussion of the factors above, my opinion is that there is insufficient evidence to conclude that other related drugs are also known to cause irreversible alopecia.

H. Conclusions Regarding the Seven Factors

164. In my opinion, a substantial number of the seven factors provided by the FDA to consider in assessing whether there is reasonable evidence of a causal association were satisfied to establish reasonable evidence of a causal association between Taxotere and irreversible alopecia by as early as 2009.¹⁸²

165. In my opinion, because a substantial number of the factors provided by the FDA to consider in assessing whether there is reasonable evidence of a causal association were satisfied as to Taxotere and irreversible alopecia by as early as 2009, and because irreversible alopecia is a serious and/or clinically significant adverse event, a Warning regarding irreversible alopecia was warranted by as early as 2009.

IX. SANOFI'S LABELING FAILED TO ADEQUATELY DISCLOSE THE RISK OF IRREVERSIBLE ALOPECIA WITH TAXOTERE

166. As acknowledged by Sanofi, prior to December 2015, Sanofi's Taxotere labeling included a reference to the adverse event of alopecia, but Sanofi never disclosed the risk of irreversible alopecia in its label or in communications with patients, physicians, or United States

(Sanofi_04876339) ("Nanae, I am okay with slides with following comments: The conclusion should be one sentence that ends with '...in patients who receive docetaxel in combination with other agents.' However, you report one case with single agent. The question then is whether we should say just 'in patients who receive docetaxel.' . . . The cases only reported docetaxel as suspect drugs are unsolicited cases; yes, only docetaxel was entered and no information in the narrative either. We will amend the conclusion as: Conclusion Proposal **The cumulative weighted evidence is sufficient to support a causal association between Docetaxel and Permanent/Irreversible alopecia in patients who receive docetaxel.**") (emphasis in original).

¹⁸² As noted above, because of the date of Taxotere administration to the bellwether plaintiffs cited above, I was asked to address these issues by as early as 2009. I reserve the right to study the issues at both earlier and later dates.

regulatory authorities¹⁸³ and internally determined that “alopecia . . . should be ‘not important risk’” in certain regulatory documents.”¹⁸⁴

167. On March 17, 2004, Sanofi submitted to FDA sNDA (S-029) in support of the following indication: use of Taxotere in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.¹⁸⁵ To support of this indication, Sanofi submitted interim analysis of 55 month follow-up data from the TAX 316 clinical trial.¹⁸⁶

¹⁸³ See, e.g., Emails between Rebecca Falcone and Gina Vestea, Aug. 20, 2012 (Sanofi_04691790) (“Do you happen to know if the HCP [health care provider] letter provides any incidence of permanent alopecia? . . . No, nothing regarding permanent alopecia. Just PI incidence.”); Email from Lynette Melman, Dec. 4, 2012 (Sanofi_01363974) (“The question is now being asked by the patient how the information regarding longstanding alopecia is communicated to doctors as it is not included in the local labeling.”); Email from Shang Jen to Nanae Hangai, Oct. 6, 2015 (Sanofi_05059732) (“My interpretation of the FDA’s request is that they would like more information in the PI regarding the details of permanent or irreversible alopecia because as of now, a vague alopecia is in the labeling with no further information.”); Email from Frances Polizzano, Oct. 6, 2015 (Sanofi_04876332) (“It should be noted that alopecia is listed as an adverse event in Section 6 Adverse Reaction (under Subsection 6.1 Clinical Trial Experience) of the Taxotere USPI and in Section 11 Adverse Reactions (under Subsection 11.1 Clinical Studies) of the Docetaxel CCDS. **However, permanent or irreversible alopecia is not listed in the Taxotere USPI nor the Docetaxel CCDS.**”) (“Since permanent or irreversible alopecia is outside the scope of the current Docetaxel CCDS . . .”) (emphasis added); Draft of 2.5 Clinical Overview: Docetaxel and Permanent Alopecia, Nanae Hangai, Oct. 29, 2015 (Sanofi_01327311) (“None of the above labeling documents contain information on permanent or irreversible alopecia.”); Sanofi Presentation on Docetaxel-Permanent/Irreversible Alopecia, Nanae Hangai and Shang Jen, Oct. 26, 2015, at p. 3 (Sanofi_01827600) (“No mention of ‘permanent or irreversible’ alopecia in USPI.”).

¹⁸⁴ See, e.g., Email from Dominique Destree to Nanae Hangai, Jan. 21, 2014 (Sanofi_01086042); (“I cannot agree that alopecia or other risks listed are considered as important risk.”); Emails between Nanae Hangai and Emanuel Palatinsky, Jan. 22, 2014 (Sanofi_01718843) (“I still think alopecia is important risk for this product, she [Dominique Destree], she does not at all.”); Email from Nanae Hangai, Jan. 23, 2014 (“She [Dominique Destree] commented that alopecia . . . should be ‘not important risk.’”); Safety Economics Part II, Emanuel Palatinsky, Nov. 2, 2011 (Sanofi_03073713) (“AEs are likely to be prevented if HCPs recognized that they could cause them” . . . “IN THEORY, ALL AEs ARE PREVENTABLE” . . . slide depicting cartoon “The good news is that we managed to save your life! The bad news is that you are going to spend it paying for the good news!”); Partnering with Your Patients Along Their Journey, Oct. 2006 (Polizzano Ex. 23; Sanofi_01038470) (“Alopecia (a-lo-PEE-shee-ah) is another word for hair loss or thinning of the hair. It is a common, yet temporary, side effect of some cancer medicines.”); Oncology Field Coaching Report of Christine Muhlenhaupt by Perry Monaco, Aug. 15 & 17, 2006 (Sanofi_04633925) (“With Dr. Sedlacek, he is bending, but not breaking The excuse of permanent alopecia is a concern of his, but should not stop him from giving TAC an opportunity.”); see also Schedule 7, Relevant Language and Revisions Made to Taxotere Labeling Related to Irreversible Alopecia.

¹⁸⁵ (Sanofi_04154773 at 1); (Sanofi_03928809 at 1).

¹⁸⁶ (Sanofi_04154773 at 1; Sanofi_03928809 at 1).

168. It appears that Sanofi submitted a proposed label as part of this sNDA.¹⁸⁷ This annotated label includes changes to the following sections of the report: Clinical Studies, Precautions, Indications and Usage, Precautions, Adverse Reactions, and Dosage and Administration.¹⁸⁸

169. The changes proposed by Sanofi to the Adverse Reactions section related to the TAX 316 clinical trial and included a chart of adverse events experienced by subjects during study treatment; paragraphs providing additional detail about certain categories of adverse events; and paragraphs describing certain adverse reactions that existed at the median follow-up time of 55 months.¹⁸⁹ With respect to the latter category, one such paragraph added by Sanofi included the following language:

Other persistent reactions

The following events were observed to be ongoing in TAC-treated patients at the medium follow-up time of 55 months: alopecia (22/687), amenorrhea (133/233), neurosensory (9/73) and peripheral edema (18/112). These events were also observed in the FAC arm during the follow-up period: alopecia (9/642), amenorrhea (101/186), neurosensory(2115) and peripheral edema (3/19).¹⁹⁰

170. On June 23, 2004, Dr. Michael Rozycki, Sanofi's Director of Oncology Regulatory Affairs and Global Regulatory Liaison for Taxotere, emailed Commander Ann Staten, FDA's Taxotere Project Manager, attaching a word document of the proposed Taxotere label for sNDA S-029.¹⁹¹ In his email, Dr. Rozycki notes the attached label contains endnotes to what are presumably references to the sNDA and uses track changes to identify proposed edits to

¹⁸⁷ (Sanofi_01296736, Sanofi_01296737).

¹⁸⁸ (Sanofi_01296737 at 18-24, 30, 35-36, 41-44, 52, 54).

¹⁸⁹ (Sanofi_01296737 at 41-44).

¹⁹⁰ (Sanofi_01296737 at 44).

¹⁹¹ (Sanofi_00355202 at 1).

the label.¹⁹² These proposed changes included the above quoted “Other persistent reactions” paragraph in the Adverse Events section.¹⁹³

171. On August 4, 2004, FDA updated Sanofi on the labeling for sNDA S-029, requesting a word version of the proposed labeling without endnotes and noting that “FDA had difficulty in using the track-changes utility with this file.”¹⁹⁴

172. Dr. Rozycki submitted the proposed label without endnotes to FDA on August 5, 2004.¹⁹⁵ This draft label included the “Other persistent reactions” paragraph in the Adverse Events section.¹⁹⁶

173. On August 9, 2004, Commander Staten at FDA contacted with Daniel Bollag, Sanofi’s Regulatory Liaison, summarizing the labeling changes requested by FDA:

Cmdr. Staten remarked that the FDA's labeling text would contain “some major revisions” in the adjuvant breast efficacy section. In addition, changes would be requested in the AE tables. She clarified further that the FDA would request that Aventis list AEs in descending order of frequency. Also, there were concerns about the way that AEs related to fluid retention were presented, which was different from the AE tables in the label for other Taxotere indications.¹⁹⁷

174. According to the Regulatory Contact Report for this communication with FDA, Commander Staten did not discuss any changes planned by FDA to the “Other persistent reactions” paragraph in the Adverse Reactions section.¹⁹⁸

¹⁹² (Sanofi_00355202 at 2-42).

¹⁹³ (Sanofi_00355202 at 30).

¹⁹⁴ (Sanofi_00559223).

¹⁹⁵ (Sanofi_00559182 at 1).

¹⁹⁶ (Sanofi_00559182 at 30).

¹⁹⁷ (Sanofi_00553474 at 2).

¹⁹⁸ (Sanofi_00553474 at 2).

175. On August 11, 2004, FDA submitted its proposed changes to the Taxotere label to Sanofi and attached a document containing “statements [that] reflect the reasoning for FDA’s changes to the TAXOTERE label.”¹⁹⁹

176. This draft label used track changes; however, because the label was produced in black and white text and not in color, the timing and authorship of the changes is not clear.

177. The draft label includes modification to the Adverse Reactions section, including deletion of all references to the median follow-up time of 55 months, including omission of the “Other persistent reactions” paragraph.²⁰⁰

178. On August 13, 2004, Dr. Bollag responded to FDA’s suggested edits to the Taxotere label with proposed modifications by Sanofi.²⁰¹ Sanofi did not add or otherwise comment on the “Other persistent reactions” paragraph or the data related to irreversible alopecia in TAX 316.²⁰²

179. Sanofi submitted its final labeling package to FDA on August 18, 2004, which included the following postmarketing commitment: “[S]ubmit a complete report of the updated TAX 316 data to verify the ... safety of Taxotere in the adjuvant treatment of women with operable node-positive breast cancer and to submit the final analysis of overall survival (expected to occur in 2010).”²⁰³

180. This same day, FDA approved sNDA 0-29 for use as “recommended in the agreed-upon labeling text.”²⁰⁴

¹⁹⁹ (Sanofi_00548479 at 1; 46-48).

²⁰⁰ (Sanofi_00548479 at 34).

²⁰¹ (Sanofi_00548432 at 1).

²⁰² (Sanofi_00548432 at 36).

²⁰³ (Sanofi_0054613 at 8); *see also* (Sanofi_00354859).

²⁰⁴ (Sanofi_00574334 at 1).

181. On August 24, 2004, Sanofi submitted its final label to the FDA.²⁰⁵ The label did not include the “Other persistent reactions” paragraph nor any reference to data related to irreversible alopecia in TAX 316.²⁰⁶

182. With respect to alopecia, the approved Taxotere label included the following statement:

Loss of hair occurs in patients taking Taxotere (including the hair on your head, underarm hair, pubic hair, eyebrows, and eyelashes). Hair loss will begin after the first few treatments and varies from patient to patient. Once you have completed all your treatments, hair generally grows back. Your doctor or nurse can refer you to a store that carries wigs, hairpieces, and turbans for patients with cancer.”²⁰⁷

183. The label had no language on persistent alopecia.²⁰⁸

184. On July 9, 2010, AFSSAPS sent Sanofi a letter requesting “a review of all of the cases of persistent alopecia.”²⁰⁹ AFSSAPS made this request after analyzing cases recorded in the National Pharmacovigilance database, published cases, and reported cases from a study presented at the 2009 SABCS conference in San Antonio, all of which found cases of irreversible alopecia significantly more prevalent in patients administered Taxotere.²¹⁰

185. In response, Sanofi performed a review of its global pharmacovigilance database, and identified 1,620 cases with HLT “Alopecia.”²¹¹ After defining the injury of irreversible

²⁰⁵ (Sanofi_04817016).

²⁰⁶ (Sanofi_04817016 at 30-31).

²⁰⁷ (Sanofi_04817016 at 6). *See also* Schedule 8, Communications between Sanofi and the FDA Regarding Proposed Language for the 2004 Label Change.

²⁰⁸ (Sanofi_04817016 at 5-42).

²⁰⁹ AFSSAPS letter, July 9, 2010 (Sanofi_03643994).

²¹⁰ *Id.* (“docetaxel is a common feature of the great majority of the cases involving chemotherapy” . . . “of the cases collected 95% of the patients have been treated with Taxotere”). Additionally, beginning in the mid-1990s and continuing through 2018, Sanofi received adverse event reports specifically relating to irreversible alopecia. *See* Depositions of Michael S. Kopreski, M.D., dated September 6, 2018 and October 11, 2018.

²¹¹ Sanofi, 2.5 Clinical Overview Docetaxel - Persistent Alopecia, January 18, 2011 (Sanofi_04353204).

alopecia to be “not recovered \geq 12 months following the last dose of chemotherapy,”²¹² Sanofi identified 142 cases (or 8.8% of those reporting HLT “Alopecia.”).²¹³ Nevertheless, Sanofi concluded to AFSSAPS that “This cumulative review of 142 reports of persistent alopecia revealed no evidence of a causal relationship with docetaxel”²¹⁴

186. On January 28, 2011, Sanofi submitted similar information to EMA regarding its next Periodic Safety Update Report (PSUR) for Taxotere.²¹⁵

187. After reviewing Sanofi’s submissions, these European regulatory authorities both concluded that “Given the serious psychological consequences of this adverse effect in, often young, patients treated mainly in the adjuvant scheme, Health care professionals and patients should be informed of the possible irreversibility of alopecia.”²¹⁶

188. The European regulatory authorities then required Sanofi to update its PSUR and EU SmPC [Summary of Product Characteristics] to “provide comparative safety results of long term follow up [from TAX 316 and GEICAM 9805/TAX 301] . . . and address th[is] risk more clearly.”²¹⁷

189. In 2013, EMA subsequently required Sanofi to update its EU SmPC to add a specific reference to “persisting” alopecia.²¹⁸

²¹² As discussed above in Section VIII(A) of this Report, although the time period in Sanofi’s 2011 analysis was \geq 12 months rather than 24 months used by Sanofi in 2015, this definition fails to conform to the definition of irreversible alopecia generally set forth in the medical literature as described in Section V. of this Report.

²¹³ Sanofi, 2.5 Clinical Overview Docetaxel - Persistent Alopecia, January 18, 2011 (Sanofi_04353204).

²¹⁴ *Id.*

²¹⁵ (Sanofi_04864365).

²¹⁶ *Id.*; (Sanofi_02540992).

²¹⁷ (Sanofi_04864365); (Sanofi_02540992).

²¹⁸ *See* Email between Sanofi and EMA, Dec. 13, 2013 (Sanofi_01026734); Sanofi Response to Agency Request, Nov. 26, 2012 (Sanofi_00811958).

190. As acknowledged by Sanofi, Sanofi failed to provide FDA with any of the data or information from its 2010-11 global pharmacovigilance database review that it provided to the European regulatory authorities, failed to provide FDA with the 2010-13 submissions or correspondence it made to these European regulatory authorities with analysis of Sanofi's internal review and, ultimately, failed to update its United States Taxotere labeling to address the risk of irreversible alopecia "more clearly" to ensure that "Health care professionals and patients [were] informed of the possible irreversibility of alopecia."²¹⁹

191. Instead, Sanofi's Taxotere labeling continued to advise patients and physicians that alopecia after completion of Taxotere was common, but "hair generally grows back."²²⁰

192. In March 2015, FDA requested "a summary of cases of permanent partial or total alopecia associated with docetaxel use."²²¹

193. In response, Sanofi performed an updated review of its global pharmacovigilance database, identifying 2,118 cases with HLT "Alopecia," and "89 cases [of the 2,118] reported verbatim including word of 'permanent' or 'irreversible', or alopecia lasted more than 2 years with outcome of not recovered/Recovering/UNK."²²² Sanofi concluded to FDA that "It was

²¹⁹ See Email from Emanuel Palatinsky, Oct. 4, 2011 (Palatinsky Ex. 21, Sanofi_04977753) (regarding need to add final TAX 316 data to United States Taxotere labeling); Email from Theresa Stathatos to Gerrit-Jan Nijveldt, Mar. 10, 2015 (Nijveldt Ex. 28, Sanofi_02983317) ("During this latest US affiliate audit I went through the Taxotere PI and found some of the findings not corrected so am not sure if they were never corrected or if they could not be."); Email from Frances Polizzano to Gina Vestea, Nov. 9, 2015 (Sanofi_05207927) ("Well this is going to be fun submitting > 4 year old labeling changes to the FDA now.").

²²⁰ See Schedule 7, Relevant Language and Revisions Made to Taxotere Labeling Related to Irreversible Alopecia; *see also* Taxotere and Persistent Alopecia, Planning for possible questions about persistent alopecia, Taxotere and Social Media Strategy, Standby Statements and Questions & Answers, Mar. 23, 2010 (Sanofi_04691789); Sanofi Consumer Information Document on Taxotere, July 2012 (Sanofi_04691845) ("Once you stop Taxotere treatment, hair generally grows back.").

²²¹ Email from Frank Cross, Jr. to Frances Polizzano, Mar. 23, 2015 (Sanofi_04878450).

²²² Sanofi Response to Agency Request, Apr. 8, 2015 (Sanofi_01259408). Sanofi used the same "2 year" timeframe as that used in Sanofi's 2015 Causation Analysis. European Medicines Agency, CHMP Type II Variation Assessment Report, May 12, 2016; Sanofi LRC Topic: Docetaxel CCDS v 30, Permanent/irreversible alopecia, Vanina Groult, Global Regulatory Affairs Labeling (GRAL), Nov. 16, 2015 (Sanofi_01101022); Sanofi, 2.5 Clinical

concluded that alopecia occurs very commonly. Permanent alopecia is mostly reported in the female patients with breast cancer. The available evidence does not show that permanent alopecia is caused by docetaxel alone.”²²³

194. In November-December 2015, FDA and Sanofi agreed to add the statement “Cases of permanent alopecia have been reported,”²²⁴ which Sanofi implemented “In accordance with 21 CFR 314.70(c) [Changes Being Effectuated].”²²⁵

195. In October 2018, FDA approved Sanofi’s April 2018 sNDA to include certain information concerning the risk of adverse events during the TAX 316 clinical trial study and adverse events that persisted following completion of that study, including but not limited to alopecia.²²⁶

196. In my opinion, by as early as 2009, Sanofi knew or should have known that there was reasonable evidence of a causal association between Taxotere and irreversible alopecia.

197. In my opinion, by as early as 2009, Sanofi knew or should have known that patients taking Taxotere were at an increased risk of irreversible alopecia compared to alternative therapies.

Overview: Docetaxel and Permanent Alopecia, November 11, 2015 (Sanofi_00829788); Sanofi Safety Management Committee Meeting Minutes, Oct. 26, 2015 (Sanofi_01827599).

Based on my review, neither the 12-month timeframe used by Sanofi in 2010-11 nor the 2-year timeframe used by Sanofi in 2015 conform to the definition of irreversible alopecia generally set forth in the medical literature as described in Section V. of this Report. As discussed above, Sanofi recognized internally that if the two-year time period was reduced, there would be more cases. Email from Nanae Hangai to Yoshiko Shimazaki and Vanina Groult, Feb. 16, 2016 (Sanofi_02664951) (“Therefore, I selected the cases: 1. If the verbatim contains ‘permanent’ or ‘irreversible’ and 2. The verbatim does not contains ‘permanent’ or ‘irreversible’ but lasted more than 2 years **(since if set less, we know we have more cases.)**”) (emphasis added).

²²³ Sanofi Response to Agency Request, Apr. 8, 2015 (Sanofi_01259408).

²²⁴ FDA PAS for alopecia, Review completed Dec. 4, 2015 for NDA #020449.

²²⁵ Letter from Frances Polizzano to FDA’s Geoffrey Kim, Nov. 24, 2015 (Hangai Ex. 18; Sanofi_03333249).

²²⁶ FDA Approval Letter to Sanofi-Aventis U.S. LLC dated October 5, 2018, at https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2018/020449Orig1s079ltr.pdf.

198. In my opinion, by as early as 2009, it was not impossible for Sanofi to include language about irreversible alopecia in its Taxotere label.

199. Based on all scientific evidence, in my opinion, by as early as 2009, Sanofi should have clearly and prominently warned patients and physicians about the risk of irreversible alopecia with Taxotere in its label.

200. In my opinion, by as early as 2009 and continuing through at least 2015, Sanofi's Taxotere labeling failed to adequately warn that there was reasonable evidence of a causal association between Taxotere and irreversible alopecia.

201. In my opinion, Sanofi's statement in its label that "hair generally grows back" was misleading when there was reasonable evidence of a causal association between Taxotere and irreversible alopecia available to Sanofi.

202. In my opinion, Sanofi's statement in its label that "hair generally grows back" was misleading when Sanofi knew or should have known that patients taking Taxotere were at an increased risk of irreversible alopecia compared to alternative therapies.

X. SANOFI'S MARKETING AND PROMOTIONAL EFFORTS TO DIFFERENTIATE TAXOTERE VERSUS TAXOL/PACLITAXEL MISLED PHYSICIANS AND DOCTORS AND PUT PATIENTS AT AN INCREASED RISK OF HARM

203. Based on my review, beginning in at least 2000 and continuing thereafter, Sanofi's marketing and promotional strategy for Taxotere was to build Taxotere into "'The First' Billion Dollar Taxane Franchise in the US" by aggressively positioning Taxotere as the foundation and cornerstone of therapy for multiple types of cancer, including breast cancer.

203.1. In its 2000 Global Marketing Strategy Document regarding Taxotere's branding, Sanofi identified its "Brand Objective" for Taxotere as: "Current Brand Position:

Sanofi: The foundation of every regimen associated with optimal survival and quality of life for a wide range of cancers.”²²⁷

203.2. In Sanofi’s Taxotere 2000-2004 Strategic Plan titled “The Cornerstone of Cancer Therapy,” Sanofi represented that its Strategic Intent was: “We believe that by aggressively marketing Taxotere’s superior clinical profile, results of phase II and III clinical trials, and by producing data in combination with novel therapeutic agents, we will position Taxotere as the cornerstone of therapy for breast, lung, prostate/bladder, SCCHN, and gastric cancer, and we will generate yearly sales of over \$500M by 2004.”²²⁸

203.3. In Sanofi’s Taxotere 2000-2004 Strategic Plan titled “The Cornerstone of Cancer Therapy,” Sanofi stated that it’s “Strategic Plan: Taxotere Breast Cancer Positioning” was “Taxotere is the cornerstone therapy in the treatment of breast cancer”²²⁹

203.4. In its 2001-2005 marketing plan detailing Sanofi’s Objectives for Taxotere, Sanofi stated that it wanted to “Position Taxotere as the cornerstone of therapy for breast, lung, prostate, ovarian, head/neck and gastric cancers,” and “Build Aventis taxane sales to \$1 billion by 2010.”²³⁰

203.5. In its 2002-2011 marketing plan for Taxotere titled “Building ‘The First’ Billion Dollar Taxane Franchise in the US,” Sanofi presented its plans to “Exceed \$1 Billion annually in 2004 and beyond.”²³¹

203.6. In its 2002-2011 marketing plan for Taxotere titled “Building ‘The First’ Billion Dollar Taxane Franchise in the US,” Sanofi stated: “Taxotere – Momentum Objectives . .

²²⁷ Global Marketing Strategy for Taxotere, 2000 (Sanofi_00749905).

²²⁸ Sanofi Taxotere 2000-2004 Strategic Plan (Sanofi_00739377) (emphasis in original).

²²⁹ *Id.*

²³⁰ Sanofi Plan 2001-2005: Taxotere-Objectives (Sanofi_00749772).

²³¹ Sanofi Plan 2002-2011: Taxotere (Sanofi_00749997).

. Position Taxotere as the cornerstone of therapy for breast, lung, prostate, ovarian, head/neck and gastric cancers Expand use of taxanes in key markets.”²³²

203.7. Sanofi’s January 19, 2005 “Strategic Product Summary” for Taxotere stated “The Ambition: Become the most successful cytotoxic ever . . . Establish Taxotere as the **cornerstone treatment** . . . Achieve WW [world-wide] sales of **2.5 billion euros** by 2008.”²³³

203.8. In Sanofi’s 2008 Presentation from the Taxotere Breast Cancer Core Team, Sanofi identified its “US Brand Strategy & Key Challenge” to “Reaffirm Taxotere’s critical role as the chemotherapy platform of choice in both early stage and metastatic breast cancer.”²³⁴

203.9. In Sanofi’s reminders to the Taxotere Marketing team following its 2009 National Sales Team Meeting, Sanofi noted that its “Key Strategy for MBC [metastatic breast cancer]” was “Defend and extend Taxotere as the choice of chemotherapy.”²³⁵

204. Sanofi recognized that Taxol/paclitaxel—another drug in the taxane class brought to market prior to Taxotere—was Taxotere’s primary competitor, and that Taxol/paclitaxel would become generic in 2001. Sanofi’s marketing and promotional strategy focused on becoming the leader of the taxane market—given the presumed decreased economic incentive for the manufacturers of Taxol and generic paclitaxel, and differentiating Taxotere from Taxol/paclitaxel to increase market share and justify Taxotere’s presumed higher price after Taxol/paclitaxel became generic.

²³² *Id.*

²³³ Sanofi Strategic Product Summary for Taxotere, January 19, 2005 (Sanofi_01500984) (emphasis in original).

²³⁴ Taxotere Breast Cancer IMAP Review, IMPACT 2008 (Sanofi_04818699).

²³⁵ (Sanofi_00791306).

204.1. In its 2000 Global Marketing Strategy Document regarding Taxotere's branding, Sanofi stated: "Current Brand Position: The second of two, essentially similar, drugs that comprise one of the most powerful classes of chemotherapy agents."²³⁶

204.2. In its 2000 Global Marketing Strategy Document regarding Taxotere's branding, Sanofi stated: "Executive Summary" for the "Breast Cancer Neoadjuvant and Adjuvant" Indication: "We are currently at a significant disadvantage in our market position in the neoadjuvant/adjuvant setting, due to the 1999 launch of BMS [Bristol Myers Squibb]'s Taxol in this very important indication. Although the early launch of Taxol was a setback, their indication does set the stage for the use of Taxanes in the treatment of early stage breast cancer." Position Taxotere as the cornerstone of therapy for 1st line MBC [metastatic breast cancer]."²³⁷

204.3. In its 2000 Global Marketing Strategy Document regarding Taxotere's branding, Sanofi stated: "Evolution of Market Pricing: Price will continue to rise in U.S. until generic Taxol entry, after which stabilization will occur."²³⁸

204.4. In its 2000 Global Marketing Strategy Document regarding Taxotere's branding, Sanofi stated: "Evolution of Reimbursement Levels: Reimbursement levels in US will continue to be challenged by insurers. Generic paclitaxel will further erode class reimbursement levels."²³⁹

204.5. In its 2000 Global Marketing Strategy Document regarding Taxotere's branding, Sanofi stated for both the "Breast Cancer Neoadjuvant and Adjuvant" Indication and "Breast Cancer First-Line Metastatic" Indication: "Pricing & Reimbursement Strategy: U.S.:

²³⁶ Global Marketing Strategy for Taxotere, 2000 (Sanofi_00749905).

²³⁷ *Id.*

²³⁸ *Id.*

²³⁹ *Id.*

Continue to annually raise prices 3-5%, drop or cease upon entry of generic paclitaxel, ROW [Rest of World]: Use economic studies to support price, use new indications to drive reimbursement. Pricing strategy is to keep US\$9.8/mg. Support positioning as superior drug to Taxol by always pricing above Taxol price. EU: continue to differentiate Taxol to support pricing.”²⁴⁰

204.6. In Sanofi’s Taxotere 2000-2004 Strategic Plan titled “The Cornerstone of Cancer Therapy,” Sanofi identified the following “Marketing Issues: External . . . Incomplete differentiation vs. paclitaxel (generic); Toxicity perceptions remain; Loyalty to paclitaxel; . . . Efficacy gains with added toxicity unacceptable”²⁴¹

204.7. In Sanofi’s Taxotere 2000-2004 Strategic Plan titled “The Cornerstone of Cancer Therapy,” Sanofi included amongst its “Marketing Issues: Internal . . . Preparation for generic paclitaxel.”²⁴²

204.8. In Sanofi’s Taxotere 2000-2004 Strategic Plan titled “The Cornerstone of Cancer Therapy,” Sanofi presented a slide titled “How Robust Are Projections That Taxotere Sales Will Hold Up Well,” which stated: “Perceived differences between Taxol and Taxotere are small; The reasons underlying use are not always clear; Lack of clear clinical advantage may raise doubt over Taxotere’s continued use (“Taxotere use will fall if its reimbursement position places it at a disadvantage to the generic); Conclusion: HMO’s and Medicare’s reimbursement of Taxotere will be critical.”²⁴³

²⁴⁰ *Id.*

²⁴¹ Sanofi Taxotere 2000-2004 Strategic Plan (Sanofi_00739377) .

²⁴² *Id.*

²⁴³ *Id.*

204.9. In Sanofi's Taxotere 2000-2004 Strategic Plan titled "The Cornerstone of Cancer Therapy," Sanofi presented a slide titled "Financial Disincentives To Use Taxotere Could Well Impact On Physician Behavior."²⁴⁴

204.10. In Sanofi's Taxotere 2000-2004 Strategic Plan titled "The Cornerstone of Cancer Therapy," Sanofi presented a slide titled: "Strategic Plan: The goal in 2000 must be to continue to differentiate . . . With . . . oncologists; managed care; Medicare . . . Continue to generate data supporting Taxotere's superiority."²⁴⁵

204.11. In its 2001-2005 marketing plan detailing Sanofi's Objectives for Taxotere, Sanofi states: "Taxotere – Key Assumptions . . . Availability of paclitaxel generics provides opportunity for Taxotere."²⁴⁶

204.12. In its 2001-2005 marketing plan detailing Sanofi's Objectives for Taxotere and its 2002-2011 marketing plan for Taxotere titled "Building 'The First' Billion Dollar Taxane Franchise in the US," Sanofi listed as a "Taxotere: Decelerator . . . Generic paclitaxel gains formulary and/or reimbursement advantage versus Taxotere . . . Key Issues: Differentiation of the taxanes; Clinical superiority established; Investment level commensurate with leadership objective."²⁴⁷

204.13. In its 2002-2011 marketing plan for Taxotere titled "Building 'The First' Billion Dollar Taxane Franchise in the US," Sanofi stated: "Plan 2002 – 2011: Taxotere Business Plan – Opening Message: . . . We are in the 'right market' with the 'right product' ant the 'right

²⁴⁴ *Id.*

²⁴⁵ Sanofi Taxotere 2000-2004 Strategic Plan (Sanofi_00739377).

²⁴⁶ Sanofi Plan 2001-2005: Taxotere-Objectives (Sanofi_00749772).

²⁴⁷ *Id.*; Sanofi Plan 2002-2011: Taxotere (Sanofi_00749997).

time’ . . . Generic paclitaxel = OPPORTUNITY . . . Aventis Oncology must ‘lead’ while ‘leadership’ is up for grabs.”²⁴⁸

204.14. In its 2002-2011 marketing plan for Taxotere titled “Building ‘The First’ Billion Dollar Taxane Franchise in the US,” Sanofi stated: “Taxotere – Key Assumptions . . . Availability of multiple paclitaxel generics launched by Q3 ’01, significantly eroding economic outlook for the multi-source drug; Taxanes continue to be standard of care for breast, lung and ovarian cancers; Aventis dominates share of voice in taxane market.”²⁴⁹

204.15. In its January 21, 2004 “Oncology MAX Team Meeting,” Sanofi presented a slide titled “Expanding Taxotere Market Leadership Strategic Objectives and Key Initiatives,” which included under “Market Share Gain: . . . Differentiate vs. Taxol.”²⁵⁰

204.16. Sanofi’s January 19, 2005 “Strategic Product Summary” for Taxotere stated “Competitive Situation: Invest to win in a challenging market . . . Paclitaxel continues to present serious market challenges (weekly / dose-dense Paclitaxel continues to grow in the US where the reimbursement system is unfavorable to Taxotere while paclitaxel generics are entering in the EU market.”²⁵¹

204.17. Sanofi’s January 19, 2005 “Strategic Product Summary” for Taxotere stated “Global Strategy: Expanding Taxotere market leadership . . . Market share gain (in the approved indications) / market expansion strategy . . . Leveraging the unique profile and

²⁴⁸ Sanofi Plan 2002-2011: Taxotere (Sanofi_00749997).

²⁴⁹ *Id.*

²⁵⁰ Sanofi Oncology MAX Team Meeting, January 21, 2004 (Sanofi_00743074).

²⁵¹ Sanofi Strategic Product Summary for Taxotere, January 19, 2005 (Sanofi_01500984).

unsurpassed clinical evidence to better differentiate versus Taxol and gain market share in MBC [metastatic breast cancer] and NSCLC [non-small cell lung cancer].”²⁵²

204.18. In Sanofi’s 2008 Presentation from the Taxotere Breast Cancer Core Team, Sanofi’s slide titled “Taxotere Breast Cancer SWOT Analysis” included under “Weaknesses . . . Perceived lack of efficacy differentiation among taxanes . . . Cost/reimbursement limitations (high cost, 3 weekly regimen, and more outlay from the patient).”²⁵³

204.19. In Sanofi’s 2008 Presentation from the Taxotere Breast Cancer Core Team, Sanofi’s slide titled “Taxotere Breast Cancer SWOT Analysis” included under “Threats . . . “Weekly paclitaxel (reimbursement, efficacy).”²⁵⁴

204.20. In Sanofi’s 2008 Presentation from the Taxotere Breast Cancer Core Team, Sanofi stated under “Key Market Dynamics”: “Although established as important components of both early stage and metastatic breast cancer therapy, multiple taxanes are available to physicians. Paclitaxel usage remains substantial based on historical precedent. Usage of FDA-approved TAC regimen in ESBC limited by perception of toxicity.”²⁵⁵

204.21. In Sanofi’s reminders to the Taxotere Marketing team following its 2009 National Sales Team Meeting, Sanofi stated: “Key Strategy MBC [metastatic breast cancer] – Defend and extend Taxotere as the choice of chemotherapy, Differentiate Taxotere as the ‘choice of chemotherapy’ backbone.”²⁵⁶

²⁵² *Id.*

²⁵³ Taxotere Breast Cancer IMAP Review, IMPACT 2008 (Sanofi_04818699).

²⁵⁴ *Id.*

²⁵⁵ *Id.*

²⁵⁶ (Sanofi_00791306).

204.22. Sanofi's 2009-2013 Strategic Brand Plan for Taxotere stated: "Taxotere was the second 'taxane' to market after Taxol (paclitaxel). Paclitaxel is now a generic product, but its legacy remains as the 'backbone' treatment of many cooperative group (which tends to influence usage in the community), and a market leader in some tumor types (NSCLC [non-small cell lung cancer], MBC [metastatic breast cancer]). The generic product has advantages in acquisition costs to the practice and lower co-pay requirements for patients. . . . Paclitaxel is Taxotere's biggest competition in ESBC [early stage breast cancer], MBC, and NSCLC."²⁵⁷

204.23. Sanofi's 2009-2013 Strategic Brand Plan for Taxotere stated: "Qualitative Opportunities: . . . Adjuvant Breast Cancer including HER2+ node + and high risk node – (per Herceptin PI) and HER2-, Increase market penetration: Differentiate Taxotere vs paclitaxel and anthracyclines."²⁵⁸

204.24. Sanofi's 2009-2013 Strategic Brand Plan for Taxotere stated: "Core competitor in ESBC [early stage breast cancer] HER 2 negative Node + disease is Paclitaxel."²⁵⁹

204.25. In a 2011 article published in Cancer Treatment Reviews, Arroyo noted the "current price differential between [docetaxel and paclitaxel] (20-fold higher for docetaxel)."²⁶⁰

204.26. Sanofi's Associate Director of Clinical Affairs, Dr. Barry Childs, testified as follows:

"Q. And by that you mean that pharmaceutical companies market and promote drugs like Taxotere when the patent exists, but when the

²⁵⁷ Sanofi's 2009-2013 Strategic Brand Plan for Taxotere, May 30, 2008 (Sanofi_04451595).

²⁵⁸ *Id.*

²⁵⁹ *Id.*

²⁶⁰ Arroyo P (2011). Controversies in the management of adjuvant breast cancer with taxanes: Review of the current literature. *Cancer Treatment Reviews* 37:105-110. *See also* Schedule 9, Published Medical Literature Used, Referenced, or Cited in Abbott's Marketing and Promotion of Taxotere.

patent expires in your experience they stop marketing the drug like they did when it was on patent?

- A. I would say for the most part what you said is true. But I think it's – it's purely, you know, a revenue generating thing. That they will not be able to obtain any revenue related to the branded drug once the patent has expired. And because of that, you know, they cannot afford the bottom line as much anymore of doing work-related to it.”²⁶¹

205. Sanofi's marketing and promotional strategy therefore focused, in part, on increasing Taxotere sales and market share by differentiating Taxotere as more efficacious, more tolerable, and just as safe or even safer than Taxol/paclitaxel.

205.1. In its 2000 Global Marketing Strategy Document regarding Taxotere's branding, Sanofi identified the “Role of the Brand” as “Taxotere delivers maximum activity and combinability with minimum negative impact on patients' daily lives.”²⁶² To differentiate Taxotere from paclitaxel (Taxol), Sanofi stated that “The Compelling Truth” is “Taxotere—alone and in combination—has not only repeatedly made a difference where paclitaxel has not, it is also more tolerable and easier to use than the ‘older’ taxane,” and “Taxotere has a better safety profile than paclitaxel—an important consideration when combining agents.”²⁶³

205.2. In Sanofi's Taxotere 2000-2004 Strategic Plan titled “The Cornerstone of Cancer Therapy,” Sanofi stated that it's “Strategic Plan: Taxotere Breast Cancer Positioning” was “Taxotere is the cornerstone therapy in the treatment of breast cancer, with significantly

²⁶¹ Deposition of Barry Childs, M.D., dated October 26, 2018, at 53:19-54:14 (objections omitted); *see also id.* at 356:8-20 (“Q. And was, to your knowledge, Bristol-Myers Squibb promoting the results of the CALGB study for paclitaxel? A. No. Q. No? A. By this time [2008] Bristol was not at all interested in whatever paclitaxel was doing. I'm sure it was a generic drug by then. Q. It had gone off patent by then? A. Yes.”).

²⁶² *Id.*

²⁶³ Global Marketing Strategy for Taxotere, 2000 (Sanofi_00749905).

superior response and survival rates as a single agent or in combination, and with a favorable safety profile.”²⁶⁴

205.3. Sanofi’s “2001 Tactical Plan” for Taxotere stated under “Key Brand Objectives”: “Continue to differentiate Taxotere from paclitaxel on the basis of efficacy, tolerability, and convenience.”²⁶⁵

205.4. In its 2001-2005 marketing plan detailing Sanofi’s Objectives for Taxotere, Sanofi noted: “Taxotere – Main Findings of Market Research/Advisory Boards/Focus Groups Conducted . . . Encourage continued promotion of the ‘difference’ and Phase III trials.”²⁶⁶

205.5. In its 2001-2005 marketing plan detailing Sanofi’s Objectives for Taxotere, Sanofi stated: “Taxotere – Core Product Strategy & Positioning . . . Positioning – Taxotere, the most active taxane, is the cornerstone of treatment in solid tumors with unmatched efficacy and tolerability, both alone and in combination with other agents, in both advanced and early stage disease.”²⁶⁷

205.6. In its 2001-2005 marketing plan detailing Sanofi’s Objectives for Taxotere and its 2002-2011 marketing plan for Taxotere titled “Building ‘The First’ Billion Dollar Taxane Franchise in the US,” Sanofi listed as a “Taxotere: Accelerator TAX 311 [a study comparing docetaxel and paclitaxel both administered every three weeks] demonstrates superiority.”²⁶⁸

205.7. In its January 21, 2004 “Oncology MAX Team Meeting,” Sanofi listed: “2003 Objectives . . . Breast cancer: Generate awareness & get buy-in of the adjuvant data while

²⁶⁴ Sanofi Taxotere 2000-2004 Strategic Plan (Sanofi_00739377) .

²⁶⁵ Sanofi 2001 Tactical Plan for Taxotere (Sanofi_00772869).

²⁶⁶ Sanofi Plan 2001-2005: Taxotere-Objectives (Sanofi_00749772).

²⁶⁷ *Id.*

²⁶⁸ *Id.*; Sanofi Plan 2002-2011: Taxotere (Sanofi_00749997).

consolidating leadership position in the metastatic setting with patient MS above taxol / file adjuvant dossier by Q4-03,” and then “Performance . . . Awareness and leadership position – achieved.”²⁶⁹

205.8. In its January 21, 2004 “Oncology MAX Team Meeting,” Sanofi presented a slide titled “Expanding Taxotere Market Leadership Strategic Objectives and Key Initiatives,” which included under “Market Share Gain: . . . Leverage the unique pharmacologic profile & unsurpassed clinical evidence – Differentiate vs. Taxol.”²⁷⁰

205.9. Sanofi’s January 19, 2005 “Strategic Product Summary” for Taxotere stated under “Recommendations to Affiliates” for “Breast” to “Leverage key monotherapy (TAX 311 [a study comparing docetaxel and paclitaxel both administered every three weeks] . . . data to secure Taxotere position as market leader in the MBC [metastatic breast cancer].”²⁷¹

205.10. In its presentation titled “One Voice: Questions anticipated following release of FY 2005 earnings / Feb 24th information meeting,” Sanofi commented on the “competitive environment and impact on Taxotere” by noting: “Generic paclitaxel (in most countries except Japan) continues to challenge the performance of Taxotere, particularly in the U.S. The head-to-head TAX 311 Taxotere vs. paclitaxel study in metastatic breast cancer, which resulted in an overall survival benefit in favor of Taxotere, remains key in demonstrating that Taxotere is clinically different from paclitaxel.”²⁷²

205.11. Sanofi’s presentation titled “Taxotere 2005: Unleash the Power,” listed under “2005-2009 Strategic Imperatives to Unleash the Power of Taxotere”: “Definitively

²⁶⁹ Sanofi Oncology MAX Team Meeting, January 21, 2004 (Sanofi_00743074).

²⁷⁰ *Id.*

²⁷¹ Sanofi Strategic Product Summary for Taxotere, January 19, 2005 (Sanofi_01500984).

²⁷² One Voice: Questions anticipated following release of FY 2005 earnings / Feb 24th information meeting (Sanofi_02012589).

Differentiate Taxotere In current indications . . . Bring our data to life to cement evidence of efficacy & tolerability of Taxotere . . . Increase MS in MBC [metastatic breast cancer]based on [TAX] 311 findings.”²⁷³

205.12. Sanofi’s presentation titled “Taxotere 2005: Unleash the Power” included a slide titled “Market Opportunity: Position TAXOTERE as a superior choice in ESBC [early stage breast cancer]” that listed under “Strategies”: “Leverage Taxotere MBC [metastatic breast cancer] survival story as a proof of concept for the use of Taxotere in ESBC.”²⁷⁴

205.13. Sanofi’s presentation titled “Taxotere 2005: Unleash the Power” included a slide titled “Market Opportunity: Position TAXOTERE as a superior choice in ESBC [early stage breast cancer]” that listed under “Action Steps / Key Tactics”: “Develop a comprehensive breast cancer historical visual aid highlighting the high efficacy of Taxotere in both MBC [metastatic breast cancer] and ESBC [early stage breast cancer] patients. (Ravdin – Valero – Tax 303 – Tax 304 – Tax 313 – Tax 311 – Tax 316).”²⁷⁵

205.14. Sanofi’s presentation titled “Taxotere 2005: Unleash the Power” included a slide titled “Market Opportunity: Maximize Taxotere leadership position in MBC [metastatic breast cancer]” that listed under “Action Steps / Key Tactics”: “Use 311 reprint carrier to transition ESBC [early stage breast cancer] / MBC call and answer both q3w and qwkly paclitaxel threat.”²⁷⁶

205.15. Sanofi’s presentation titled “Taxotere 2005: Unleash the Power” included a slide titled “Post ESBC [early stage breast cancer] launch integrated sales call: NO TRADE-

²⁷³ Taxotere 2005: Unleash the Power (Sanofi_04666990).

²⁷⁴ *Id.*

²⁷⁵ *Id.*

²⁷⁶ *Id.*

OFFS MBC [metastatic breast cancer] & ESBC” that stated under “Objective”: “Provide combined sales materials” and “NO TRADE-OFFS means a full BREAST CANCER sales call.”²⁷⁷

205.16. Sanofi’s March 31, 2005 “Tactical Plan: Breast Team” stated under “Market Opportunity: Position TAXOTERE after launch as the preferred choice in ES [early stage]” with “Strategies” that included “Leverage Taxotere’s MBC [metastatic breast cancer] survival story to drive it’s adoption in adjuvant setting.”²⁷⁸

205.17. Sanofi’s March 31, 2005 “Tactical Plan: Breast Team” stated in a slide titled “Alignment of Medical Drivers with Strategies is Critical” that “Marketing Strategies” included “ESBC [early stage breast cancer]: Leverage MBC [metastatic breast cancer] Story” and “MBC: Leverage [TAX] 311” and then as “Medical Drivers” for both of these “Marketing Strategies” listed “Generate and communicate key clinical data in all stages of breast cancer.”²⁷⁹

205.18. Sanofi’s March 31, 2005 “Tactical Plan: Breast Team” stated in a slide titled “Alignment of Medical Drivers with Strategies is Critical” that “Marketing Strategies” included “ESBC [early stage breast cancer]: Address Toxicity” and then as a corresponding “Medical Driver” provided “Differentiate toxicity and QOL [quality of life] profiles of Taxanes in breast cancer.”²⁸⁰

205.19. In Sanofi’s “Smart Group Minutes” from February 28, 2006 regarding Taxotere’s “Core Mission,” Sanofi stated under “Define Message: Position statement brainstorm

²⁷⁷ *Id.*

²⁷⁸ Sanofi’s Breast Cancer Strategic Review, March 31, 2005 (Sanofi_05665331).

²⁷⁹ *Id.*

²⁸⁰ *Id.*

. . . Predictable, management safety profile . . . You know Taxotere is effective. We know Taxotere also has toxicities but we are going to help you manage them.”²⁸¹

205.20. In Sanofi’s Oncology Field Coaching Report of Christine Muhlenhaupt, a sales representative calling on Dr. Sedlacek, the author of a 2006 study finding that 6.3% of patients experienced irreversible alopecia with Taxotere,²⁸² Sanofi District Manager Perry Monaco stated: “With Dr. Sedlacek, he is bending, but not breaking. He informed you that he is no longer using dose dense for [his] er+ patients, but is now using traditional AC followed by Taxol. There is no reason why this should have been his regimen of choice. The excuse of permanent alopecia is a concern of his, but should not stop him from giving TAC an opportunity. . . . Don’t let him off the hook!!!!!!”²⁸³

205.21. In Sanofi’s 2007 Taxotere Tactics: Recommendations for Breast Indications presentation, Sanofi stated under “Strategic Imperatives” for “ESBC [early stage breast cancer]”: Position as ‘kinder’—no chronic toxicities.”²⁸⁴

205.22. In Sanofi’s 2007 Taxotere Tactics: Recommendations for Breast Indications presentation, Sanofi presented a slide titled “Establish Manageability of Taxotere,” which included the “Look Good/Feel Better Program” that would “Provide Kits, that could be handed out at national events. Kits could include: Nail Kits, Scarves, Blankets, Pink Diaries, Makeup specifically created for patients undergoing chemotherapy.”²⁸⁵

²⁸¹ Smart Group Minutes, Feb. 28, 2006 (Sanofi_04508007).

²⁸² See Sedlacek SW, Persistent Significant Alopecia (PSA) form Adjuvant Docetaxel after Doxorubicin/Cyclophosphamide (AC) Chemotherapy in Women With Breast Cancer. Presented at the Annual San Antonio Breast Cancer Symposium, December 14-17, 2006.

²⁸³ Oncology Field Coaching Report of Christine Muhlenhaupt by Perry Monaco, Aug. 15 & 17, 2006 (Sanofi_04633925).

²⁸⁴ Life Brands: 2007 Taxotere Tactics, Recommendations for Breast Indications (Sanofi_04490670).

²⁸⁵ *Id.*

205.23. In Sanofi's 2007 Taxotere Tactics: Recommendations for Breast Indications presentation, Sanofi presented a slide titled "Establish Manageability of Taxotere," which included a section on "Nurse Counseling Resource" that would "Elevate role of Oncology nurses when educating patients on disease state and adverse event management."²⁸⁶ Regarding the adverse effect of alopecia, Sanofi was informing nurses (and patients) that alopecia is a "common, yet temporary, side effect of some cancer medications," and "hair should grow back once you stop treatment."²⁸⁷

205.24. In its 2008 Breast Cancer Brand Plan, Sanofi states under a slide titled "MBC [metastatic breast cancer] Core Strategic Imperatives/Operational Initiatives/Resources": "Differentiation vs paclitaxel, multiple Taxane formulations and other competitors" and included as "Key Messages": "Proven survival vs paclitaxel (Jones) [the 2005 Jones article noted below regarding Sanofi's TAX 311 study]".²⁸⁸

205.25. In Sanofi's 2008 Presentation from the Taxotere Breast Cancer Core Team, Sanofi stated: "US Brand Vision . . . To the oncologist treating breast cancer in the adjuvant setting, Taxotere (TAC) provides significantly longer DFS [disease free survival and longer OS [overall survival]. Risk of recurrence reduced regardless of prognostic factors, with a well established safety profile."²⁸⁹

²⁸⁶ *Id.*

²⁸⁷ Partnering with Your Patients Along Their Journey, Oct. 2006 (Polizzano Ex. 23; Sanofi_01038470) ("Alopecia (a-lo-PEE-shee-ah) is another word for hair loss or thinning of the hair. It is a common, yet temporary, side effect of some cancer medicines."); Talking About Taxotere, Answers to Important Questions About Your Treatment, for patients (Sanofi_00741049) ("Hair Loss . . . **However, your hair should grow back once you stop treatment.**") (emphasis in original); *see also* Sanofi's Oct. 16, 2006 Taxotere Patient Information Leaflet (Nijveldt Ex. 32) (Under "What are the possible side effects of Taxotere," included "Hair Loss . . . Once you have completed all your treatments, hair generally grows back.").

²⁸⁸ Sanofi 2008 Breast Cancer Brand Plan (Sanofi_04460197).

²⁸⁹ Taxotere Breast Cancer IMAP Review, IMPACT 2008 (Sanofi_04818699).

205.26. In Sanofi's 2008 Presentation from the Taxotere Breast Cancer Core Team, Sanofi stated: "Taxotere Breast Cancer Product Profile . . . Superior median overall survival to paclitaxel (TAX 311) . . . Superior RR [response rate] in the ITT population and superior TPP [time to progression] in both evaluable and ITT [intent to treat] population."²⁹⁰

205.27. In Sanofi's 2008 Presentation from the Taxotere Breast Cancer Core Team, Sanofi's slide titled "Taxotere in Breast Cancer: Medical Rationale" included "Superior efficacy when compared to Q3 Week Paclitaxel in MBC [metastatic breast cancer] and Adjuvant BC [breast cancer]."²⁹¹

205.28. In Sanofi's 2008 Presentation from the Taxotere Breast Cancer Core Team, Sanofi's stated: "Medical Value & Stakeholder Barriers for Physicians . . . Address/Counter weekly Paclitaxel & Abraxane challenges . . . Inability to embrace safety/efficacy data differentiating Taxotere, Abraxane and Paclitaxel . . . [and then TAX] 311 data in MBC [metastatic breast cancer] establishes efficacy versus Paclitaxel."²⁹²

205.29. In Sanofi's reminders to the Taxotere Marketing team following its 2009 National Sales Team Meeting, Sanofi stated: "Key Reminders from the Breast Workshops: . . . MBC [metastatic breast cancer]: . . . Jones et al [regarding Sanofi's TAX 311 study] Reprint Carrier."²⁹³

205.30. Sanofi's 2009-2013 Strategic Brand Plan for Taxotere stated under "Growth Drivers" for "Metastatic Breast Cancer": . . . Leverage the Taxotere efficacy versus

²⁹⁰ *Id.*

²⁹¹ *Id.*

²⁹² *Id.*

²⁹³ (Sanofi_00791306).

paclitaxel (head-to-head TAX311 study to differentiate Taxotere from paclitaxel / nab-paclitaxel in metastatic breast cancer).”²⁹⁴

205.31. In its Taxotere Branding Tool Kit, Version 1.0, Sanofi states: “Key Brand Messages – Breast cancer (early-stage) – Positioning – Taxotere in combination with an anthracycline-based regimen is a *new standard of care* for node-positive, early-stage breast cancer (ESBC) patients because it provides significant 5-year disease free and overall survival advantages and has a generally predictable and manageable safety profile.”²⁹⁵

205.32. In its Taxotere Branding Tool Kit, Version 1.0, In its Taxotere Branding Tool Kit, Version 1.0, Sanofi states: “Key Brand Messages – Overall core messages: The first Taxotere-based adjuvant regimen to demonstrate significant advantage in disease-free survival and overall survival in women with early-stage, node-positive breast cancer . . . ; Generally predictable and manageable safety profile; Most convenient taxane available.”²⁹⁶

205.33. In its Taxotere Branding Tool Kit, Version 1.0, Sanofi’s “Key Promotional Messages” for its TAX 316 clinical trial included “Adding Taxotere to anthracycline regimens for early breast cancer improves survival with manageable toxicity, and no impact on quality of life.”²⁹⁷ The “Safety” from the TAX 316 clinical trial provided in its Branding Tool Kit includes data regarding neutropenia and infections, but does not include any data, information or references to the TAX 316 irreversible alopecia data.²⁹⁸

²⁹⁴ Sanofi’s 2009-2013 Strategic Brand Plan for Taxotere, May 30, 2008 (Sanofi_04451595).

²⁹⁵ (Sanofi_04534603).

²⁹⁶ *Id.*

²⁹⁷ *Id.*

²⁹⁸ *Id.*; see TAX 316 Interim Clinical Study Report, Jan. 21, 2004 (Sanofi_02640580); TAX 301/GEICAM 9805 Interim Clinical Study Report, Jan. 30, 2004 (Sanofi_00799397); TAX 316 Clinical Study Report, Sept. 9, 2010 (Sanofi_02645200).

205.34. In its Taxotere Branding Tool Kit, Version 1.0, Sanofi provides the following regarding its TAX 311 study: “Overall: Taxotere offers a proven survival advantage over paclitaxel in metastatic breast cancer in the first and only direct clinical comparison of taxanes . . . Efficacy: Superior overall survival with Taxotere vs. paclitaxel (intent-to-treat); . . . Significantly longer time to disease progression with Taxotere vs paclitaxel; . . . Higher overall response with Taxotere vs. paclitaxel . . . Safety: . . . Safety profile of Taxotere in this patient population is well characterized.”²⁹⁹

206. However, during this timeframe, and as cited by regulatory authorities, Sanofi knew or should have known that it lacked any evidence to support its marketing and promotional strategy seeking to differentiate Taxotere versus Taxol/paclitaxel—including its reliance on the TAX 311 study, that its claims regarding Taxotere’s superiority and efficacy compared with Taxol/paclitaxel were “unsubstantiated” and “misleading,” and that Sanofi’s internal documents acknowledged and published medical literature found that there was little differentiation between these taxanes and even evidence that Taxol/paclitaxel was just as or even more efficacious than Taxotere, more tolerable than Taxotere, and less toxic than Taxotere.

206.1. As noted above, in Sanofi’s Taxotere 2000-2004 Strategic Plan titled “The Cornerstone of Cancer Therapy,” Sanofi presented a slide titled “How Robust Are Projections That Taxotere Sales Will Hold Up Well,” which stated: “Perceived differences between Taxol and Taxotere are small; The reasons underlying use are not always clear; Lack of clear clinical advantage may raise doubt over Taxotere’s continued use”³⁰⁰

206.2. Sanofi’s January 19, 2005 “Strategic Product Summary” for Taxotere provided a SWOT analysis that among Taxotere’s “Weaknesses” listed “Incomplete

²⁹⁹ (Sanofi_04534603).

³⁰⁰ Sanofi Taxotere 2000-2004 Strategic Plan (Sanofi_00739377) .

differentiation vs. Taxol” and among its “Threats” listed “Emergence of widely available generic Taxol/paclitaxel across major markets,” “Taxane reimbursement policies favoring (generic) paclitaxel where strong differentiation has not been achieved,” and “Weekly / dose dense paclitaxel regimens intensify its usage among prescribers.”³⁰¹

206.3. In Sanofi’s 2008 Presentation from the Taxotere Breast Cancer Core Team, Sanofi stated: “Key SWOT Elements: Weaknesses – Perceived lack of efficacy differentiation among taxanes; Toxicity (perception, neutropenia, neuropathy, asthenia, alopecia, hyperlacrimation, fluid retention, nail toxicities).”³⁰²

206.4. In Sanofi’s 2008 Presentation from the Taxotere Breast Cancer Core Team, Sanofi stated: “Taxotere Breast Cancer: Executive Summary – Key Medical Challenges: Superiority of Taxotere to Paclitaxel in ESBC [early stage breast cancer] and MBC [metastatic breast cancer] confirmed only vis-avis Q3w schedule of paclitaxel . . . Lack of head-to-head data with weekly paclitaxel and Abraxene.”³⁰³

206.5. Sanofi’s 2009-2013 Strategic Brand Plan for Taxotere stated under the section titled “ESBC [early stage breast cancer] Her2 negative, Node + and Node negative disease: (Adjuvant Breast Cancer)”: “Most recent publication of E1199 cooperative group clinical trial indicated that weekly AC/paclitaxel was superior to Q3w, AC/Taxotere compared favorably on DFS [disease free survival] and specifically in ER/PR positive disease.”³⁰⁴

³⁰¹ Sanofi Strategic Product Summary for Taxotere, January 19, 2005 (Sanofi_01500984).

³⁰² Taxotere Breast Cancer IMAP Review, IMPACT 2008 (Sanofi_04818699).

³⁰³ Taxotere Breast Cancer IMAP Review, IMPACT 2008 (Sanofi_04818699).

³⁰⁴ Sanofi’s 2009-2013 Strategic Brand Plan for Taxotere, May 30, 2008 (Sanofi_04451595).

206.6. Sanofi's 2009-2013 Strategic Brand Plan for Taxotere stated "There is not a great deal of perceived difference between paclitaxel and Taxotere with 'less neuropathy' and 'survival benefit' being possible points of differentiation."³⁰⁵

206.7. On April 16, 2009, DDMAC³⁰⁶ sent Sanofi a letter relating to a reprint carrier that included a reprint from the Journal of Clinical Oncology describing Sanofi's clinical trial TAX 311.³⁰⁷ Sanofi's TAX 311 trial studied the efficacy benefits of Taxotere versus paclitaxel (Taxol).³⁰⁸ DDMAC concluded that Sanofi's promotional material was misbranded in violation of the FDCA in that it was false and misleading because it presented "unsubstantiated superiority claims and overstates the efficacy of Taxotere."³⁰⁹ Specifically, DDMAC found that the claims of Taxotere's significantly higher response rates, significantly longer duration of response, significantly longer median overall survival, significantly longer median time to progression compared to Taxol "misleadingly suggest that Taxotere is superior to paclitaxel in

³⁰⁵ *Id.*

³⁰⁶ Separately, DDMAC cited Sanofi on two other occasions for distributing marketing and promotional materials in violation of the FDCA. *See* Letter from DDMAC's Joseph Grillo to Sanofi's Kerry Rothschild, Dec. 18, 2002 (Gaydos Ex. 5) ("These promotional pieces are false or misleading because they omit material facts with regard to the indication for Taxotere, make misleading efficacy claims, and omit safety information."); Letter from DDMAC's Thomas Abrams to Sanofi's Gerald Belle, Nov. 12, 2003 (Sanofi_008539) ("These DTC [direct-to-consumer] ads misleadingly overstate the survival benefits of Taxotere and imply that survival depends on treatment with Taxotere, while also minimizing the serious and potentially life-threatening risks associated with the drug by omitting some risk information and presenting other risk information in an inconspicuous manner.").

³⁰⁷ Letter from DDMAC's to Sanofi's MaryRose Salvacion, Apr. 16, 2009 (Sanofi_01302842).

³⁰⁸ *Id.*; Jones SE. (2005). Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol* 23(24):5542-51. The Authors' Disclosures of Potential Conflicts of Interest indicates that of the article's 15 authors, 12 were consultants for, held stock in, receiving Honoria from, or received other compensation from Aventis, Sanofi, or Sanofi Aventis. *Id.* Sanofi funded the authors of additional studies aimed at highlighting the benefits of docetaxel compared to competitor drugs. *See also, e.g.,* Bernard L.M. (2011). A Canadian economic analysis of U.S. Oncology Adjuvant Trial 9735. *Curr Oncol* 18(2):67-75 (concluding that "[c]ost effectiveness, combined with efficacy and an acceptable safety profile, support the adoption of TC [docetaxel and cyclophosphamide) as an alternative to AC [doxorubicin and cyclophosphamide] in Canadian clinical practice for the adjuvant treatment of operable early breast cancer" in an article written by Cornerstone Research Group Inc., an organization "contracted by Sanofi-Aventis Canada to develop the health economic model and to conduct the economic evaluation. Sanofi-Aventis was solely responsible for the funding of the all components of the study" and further noting that certain authors were consultants and have received Honoria and unrestricted funding from Sanofi).

³⁰⁹ Letter from DDMAC's to Sanofi's MaryRose Salvacion, Apr. 16, 2009 (Sanofi_01302842).

the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy, and overstate the efficacy of Taxotere. FDA is unaware of substantial evidence to support these claims.”³¹⁰

206.8. Sanofi’s Associate Director of Clinical Affairs, Dr. Barry Childs, testified as follows:

“Q. When you were at Sanofi, you did understand that the company wanted to use the TAX311 data to promote the efficacy of Taxotere over Taxol, right?

A. At some point in my tenure there, yes.

...

Q. And the reason they wanted to promote the drug, is so their physicians would use the drug, right?

A. Yes, I think that’s a fair conclusion, yeah.

...

Q. While you were at Sanofi, did you see any studies that indicated to you that Taxotere was more efficacious than Taxol in treating breast cancer?

A. Clinical studies?

Q. Yes, sir.

A. No.

Q. Since you’ve left Sanofi [in 2012], have you seen any studies that indicate to you that Taxotere is superior to Taxol with regard to efficacy?

³¹⁰ *Id.* The reprint was authored by, among others, Sanofi employees and consultants. Despite FDA’s concerns regarding the misleading nature of the reprint, the article was neither withdrawn nor amended and, to date, has been cited in many other publications as authoritative. *See, e.g.,* Berlfiglio M. (2012). Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in metastatic breast cancer. *Journal of Cancer Research and Clinical Oncology* 138(2): 221-229; *see also* Deposition of Dr. Barry Childs, October 26, 2018 at 81:23- 82:8 (“Q. Was it the situation with the TAX311 reprint that despite the review committees lack of unanimous agreement, that high level executives overrode that and decided that the print should be used? A. Such an appeal process was in place and I believe that was what was done here.”) (objection omitted).

A. No.”³¹¹

206.9. In a 2008 article published in the New England Journal of Medicine comparing “the efficacy of two different taxanes, docetaxel and paclitaxel, given either weekly or every 3 weeks, in the adjuvant treatment of breast cancer,” Sparano et al. concluded that “[W]eekly paclitaxel after standard adjuvant chemotherapy with doxorubicin and cyclophosphamide improves disease-free and overall survival in women with breast cancer.”³¹²

206.10. In a 2010 article published in Cancer Treatment Reviews, Arroyo et al. noted that “Against the backdrop of a major increase in the use of docetaxel rather than paclitaxel in our setting over the past few years, implying a major increase in costs, we examined whether this higher use of docetaxel is supported by the available evidence” and found, based on a review of “sixteen randomized clinical trials, three meta-analyses, one systematic review, and five clinical practice guidelines” that “In this wide study, we found no evidence that regimens containing docetaxel yield greater benefits than those including paclitaxel. From an effectiveness standpoint, the change from paclitaxel to docetaxel is not justified.”³¹³ Arroyo further wrote: “NCCN [National Comprehensive Cancer Network], CCO [Cancer Care Ontario], and ESMO [European Society for Medical Oncology] guidelines do not prioritize one taxane over another.”³¹⁴

³¹¹ Deposition of Barry Childs, M.D., dated October 26, 2018, at 176:5-180:19 (objections omitted).

³¹² Sparano J. (2008). Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer. *New England Journal of Medicine* 358:16. Sparano also found “no significant differences in survival between the groups treated with paclitaxel and those treated docetaxel or between the groups treated weekly and those treated every 3 weeks.” *Id.*

³¹³ Arroyo P. (2010). Controversies in the management of adjuvant breast cancer with taxanes: Review of the current literature. *Cancer Treatment Reviews* 37:105-110.

³¹⁴ *Id.* (But noting that NICE [National Institute for Health and Clinical Experience] guidelines do not include paclitaxel among its recommendations because of a lack of a systematic review).

206.11. In a 2013 article published in *Current Medical Research and Opinion*, Qi et al. sought to perform a “meta-analysis of randomized controlled trials to compare the safety and efficacy of [docetaxel and paclitaxel] in MBC [metastatic breast cancer].”³¹⁵ The authors reviewed seven eligible trials involving 1,694 patients with MBC, and concluded that “The present systematic review and meta-analysis demonstrates that both taxane-based regimens have comparable efficacy for patients with MBC [metastatic breast cancer], and the paclitaxel-based regimen is associated with less toxicity and better tolerability, especially in older patients and when used in weekly regimens.”³¹⁶

206.12. In a 2015 article published in *Cancer Treatment Reviews*, Carbognin et al. reviewed data from 15 trials (3,601 patients) to address questions regarding the “difference in terms of activity and tolerability” between paclitaxel and docetaxel.³¹⁷ The authors found that “Although the activity of neoadjuvant paclitaxel and docetaxel HER2-positive breast cancer is considered similar, the slight advantage in pCR [pathological complete response], the significantly lower neutropenia and FN [febrile neutropenia], do favor paclitaxel (in the weekly fashion) over docetaxel, despite the slightly worst neurotoxicity.”³¹⁸

206.13. In a 2015 abstract published in the *Chinese Journal of Oncology*, Wei et al. sought to “analyze the efficacy and safety of paclitaxel liposomal and docetaxel for

³¹⁵ Qi W (2013). Paclitaxel-based versus docetaxel based regimens in metastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Current Medical Research & Opinion* 29 (Vol. 2): 117-125.

³¹⁶ *Id.* (But noting that a “sub-group analysis based on previous treatment for MBC” . . . “found that a paclitaxel-based regimen significantly improved OS [median overall survival] compared with a docetaxel-based regimen as first-line treatment for MBC.”).

³¹⁷ Carbognin L. (2015). Balancing activity and tolerability of neoadjuvant paclitaxel- and docetaxel-based chemotherapy for HER2-positive early stage breast cancer: Sensitivity analysis of randomized trials. *Cancer Treatment Reviews* 41:262-270.

³¹⁸ *Id.*

neoadjuvant chemotherapy of breast cancer.”³¹⁹ The authors concluded that “Compared with docetaxel, paclitaxel liposome has the same anti-tumor efficacy, but causes fewer and milder adverse reactions with a higher safety in the neoadjuvant chemotherapy for breast cancer.”³²⁰

207. In my opinion, Sanofi’s marketing and promotional efforts to differentiate Taxotere versus Taxol/paclitaxel using “unsubstantiated” and “misleading” claims about Taxotere’s efficacy, safety, and tolerability and Taxotere’s superiority versus Taxol/paclitaxel misled physicians and doctors and put patients at an increased risk of harm.

XI. CONCLUSIONS

208. In Summary, in my opinion and for the reasons set forth in this Report:³²¹

208.1. Irreversible alopecia meets the criteria for a serious and/or clinically significant adverse event because of the distressing nature of this injury and its profound impact on mental health, physical, psychosocial and psychological distress, quality of life, patient compliance, and patient willingness to undergo chemotherapy or instead choose a different therapy or treatment, and the absolute risk or rate of occurrence of this adverse reaction.

208.2. A substantial number of the factors provided by the FDA to consider in assessing whether there is reasonable evidence of a causal association were satisfied to establish reasonable evidence of a causal association between Taxotere and irreversible alopecia by as early as 2009.

208.3. Because a substantial number of the factors provided by the FDA to consider in assessing whether there is reasonable evidence of a causal association were satisfied as to Taxotere and irreversible alopecia by as early as 2009, and because irreversible alopecia is

³¹⁹ Wei S. (2015). Efficacy and safety analysis of paclitaxel liposomal and docetaxel for the neoadjuvant chemotherapy of breast cancer. *Chin J Oncol* 37(5):379-382.

³²⁰ *Id.*

³²¹ This section is not meant as an all-inclusive list of my opinions. For all opinions, please see the Report.

a serious and/or clinically significant adverse event, a Warning regarding irreversible alopecia was warranted by as early as 2009.

208.4. By as early as 2009, Sanofi knew or should have known that there was reasonable evidence of a causal association between Taxotere and irreversible alopecia.

208.5. By as early as 2009, Sanofi knew or should have known that patients taking Taxotere were at an increased risk of irreversible alopecia compared to alternative therapies.

208.6. By as early as 2009, it was not impossible for Sanofi to include language about irreversible alopecia in its Taxotere label.

208.7. Based on all scientific evidence, by as early as 2009, Sanofi should have clearly and prominently warned patients and physicians about the risk of irreversible alopecia with Taxotere in its label.

208.8. By as early as 2009 and continuing through at least 2015, Sanofi's Taxotere labeling failed to adequately warn that there was reasonable evidence of a causal association between Taxotere and irreversible alopecia.

208.9. Sanofi's statement in its label that "hair generally grows back" was misleading when there was reasonable evidence of a causal association between Taxotere and irreversible alopecia available to Sanofi.

208.10. Sanofi's statement in its label that "hair generally grows back" was misleading when Sanofi knew or should have known that patients taking Taxotere were at an increased risk of irreversible alopecia compared to alternative therapies.

208.11. Sanofi's marketing and promotional efforts to differentiate Taxotere versus Taxol/paclitaxel using "unsubstantiated" and "misleading" claims about Taxotere's

efficacy, safety, and tolerability and Taxotere's superiority versus Taxol/paclitaxel misled physicians and doctors and put patients at an increased risk of harm

A handwritten signature in black ink, appearing to read 'D. Kessler', written over a horizontal line.

David A. Kessler, M.D.

11 / 6 /2018
Date

EXHIBIT K

Filed Under Seal

EXHIBIT K

**In re: Taxotere (Docetaxel) Products Liability Litigation
(MDL No. 2740)**

Expert Report of John Glaspy, M.D.

Date Submitted: December 14, 2018

INTRODUCTION

I have been asked to analyze medical and scientific literature and to apply my research and clinical experience to formulate opinions regarding the development, use, efficacy, and side effects of chemotherapeutic drugs used to treat women diagnosed with breast cancer. I have also been asked to review the individual cases of Ms. Durden, Ms. Francis, and Ms. Earnest, and to provide my opinions with respect to plaintiffs' expert reports addressing these issues and/or chemotherapy and breast cancer patients generally.

I am familiar with alopecia occurring in women treated with chemotherapy and have treated thousands of women with breast cancer in my career. All of my opinions expressed in this report are stated to a reasonable degree of medical and scientific probability, and are based on my review of the relevant literature, my decades of experience as a practicing hematologist/medical oncologist, a professor of oncology, and a researcher in these areas.

A list of documents I considered in connection with this report is attached as **Exhibit A**. My *Curriculum Vitae*, which lists my publications for over the last 10 years, is attached as **Exhibit B**. A list of my testimony for the last four years is attached as **Exhibit C**. My hourly rate is \$400 for general work and \$400 per hour for trial testimony. My compensation is not contingent on the opinions expressed in this report or the outcome of this litigation.

EDUCATION AND PROFESSIONAL BACKGROUND

I am a medical oncologist and a professor of medicine at UCLA Jonsson Comprehensive Cancer Center in Los Angeles, California. My clinical practice, for 34 years, has been the treatment of cancer – with a focus on breast cancer and melanoma.

I received a M.D. from the University of California, Los Angeles (UCLA) in 1979, where I also completed an internship in 1980. Following my internship, I completed a residency in internal medicine in 1982 and a fellowship in hematology and oncology at UCLA in 1985. I am board-certified in internal medicine (1982), hematology (1986), and medical oncology (1985). I am a member the American Society of Clinical Oncology, the Southwest Oncology Group, the American Federation for Clinical Research, the International Society of Interferon Research, and the American Society of Nuclear Medicine.

I have worked on numerous clinical trials involving chemotherapy drugs to determine, among other end points, which chemotherapeutic regimens are the most effective. I have published close to 300 articles over the course of my career and have been named to the list of "Best Doctors in America." A major focus of my oncologic practice for the past 34 years has been, and still is, devoted to the treatment of woman diagnosed with breast cancer.

I. GENERAL OPINIONS

Overview of Breast Anatomy and the Lymphatic System

I will offer opinions and testimony about the anatomy of the breast and lymphatic system. The breast is the tissue that sits on top of the pectoralis (“pec”) chest muscle. Although composed mainly of fatty tissue (adipose tissue), women’s breasts contain specialized tissue called lobes (made up of many smaller lobules) that connect to milk ducts that act as conduits to carry milk to the nipple. The adipose tissue extends from the edge of the sternum (flat bone in the middle of the chest) down to the underarm and across the middle of the ribcage. A healthy female breast will have up to 20 lobes. The fatty tissue and ligaments provide support to the breast and give it shape. The breast also contains nerve tissues, blood vessels, lymph vessels, and lymph nodes.

The lymphatic system is a network of drainage channels throughout the body connecting through lymph nodes, and ultimately, to the blood stream. Lymph is the excess fluid that is not absorbed by veins and is formed in body tissues. The lymphatic system also plays an essential role in an individual’s immune system, with the lymph nodes serving as centers for white blood cell differentiation, targeting, and activation. Lymphatic vessels act as sump drains that collect excess fluid in the tissues and return it to the blood stream.¹ Lymphatic vessels are important in transporting immune cells and fluids, and acting as filters that collect potential targets for an immune reaction (bacteria, viruses and possibly tumor cells). The lymphatic system of the breast is relevant to the treatment of breast cancer.

Breast Cancer Overview

I will offer opinions and testimony about cancer and breast cancer. Cancer is the name given to a group of diseases signified by the uncontrolled growth of a single cell. Cancer is the second-leading cause of death in the United States. Breast cancer is the single most prevalent form of cancer in the United States.

Cancer cells can arise almost anywhere in the human body and are different from normal cells, due to multiple mutations, in that they continue to divide without stopping, and can colonize and grow in distant parts of the body. Cancer cells are able to resist a process known as apoptosis (programmed cell death), which the body uses to eliminate defective or mutated cells. This uncontrolled growth of cells is made possible by mutations in DNA, which damage the cell’s “instruction book” that regulates its behavior. Genetic mutations can cause a cell to grow and divide more rapidly without normal cessation of cell division and to create new cells that have the same mutations. Cancer cells can establish their own blood supply, and, if not treated, divide and spread until they kill the host. The individual behavior of a cancer is determined by the loss or gain in gene expression resulting from the

¹ Lymphatic vessels are similar to small veins that carry lymph fluid away from the breast.

accumulated mutations. The more aggressive the cancer cell, the higher chance it will invade local tissue and travel, via a process known as metastasis, to vital organs. There they disrupt normal organ function and can cause death.

The most common type of cancer among women in the United States is breast cancer. Breast cancer develops in the ducts or lobules of the breast and can happen in males, although it is much more common in women. When an early breast cancer penetrates the wall of the breast duct or lobule it enters the body and is known as invasive carcinoma. Cancer cells that have arisen in the lobules and entered the body are known as invasive lobular carcinoma; those arising in the ducts and penetrating the body are known as invasive ductal carcinoma. Invasive ductal and lobular carcinomas are the most common forms of breast cancer. Invasive ductal carcinoma comprises approximately 80% of all invasive breast cancers while 10% are invasive lobular. Once invasive, breast cancer can spread outside the breast through blood vessels and lymph vessels.

Prevalence and Risk Factors for Breast Cancer

I will discuss the prevalence of and risk factors for breast cancer. Currently, about 1 in 8 women (12%) will be diagnosed with breast cancer in their lifetime. In comparison, about 1 in 17 (5.9%) women will develop lung cancer, 1 in 23 (4.3%) women will develop colon cancer, and 1 in 75 (1.3%) women will develop ovarian cancer. Each year approximately 170,000 women will be diagnosed with breast cancer in the United States. More than 3 million women are living with breast cancer in the United States. Approximately 55,000 women will die each year from this disease.

The strongest risk factor for breast cancer is female gender. Among women, the strongest risk factor is age. The median age of first diagnosis of breast cancer is 61. Seventy percent of new breast cancer cases occur in women over 55 years old. Women who have inherited mutations to genes, such as BRCA1 and BRCA2 have an increased risk of breast cancer. Other factors that may increase a women's risk for breast cancer include a family history of breast cancer, reproductive history (age at first pregnancy), environmental factors (smoking, chemicals), increased exposure to estrogen (early menarche or late menopause) a prior history of breast cancer, and previous treatment with radiation therapy to the chest or breast area.

Breast Cancer Diagnosis

I will discuss breast cancer screening and diagnosis. Women of any age are at risk for breast cancer. Because early detection is important, women are counseled to keep yearly physician appointments, which should include a routine breast examination.

Breast cancer can present as a mass in the breast; other symptoms of breast cancer can include a change in the size, shape, or appearance of the breast such as: changes in the breast skin (breast dimpling), the breast nipple becoming inverted, scaling, peeling or

flaking of the skin on the breast, or discharge from the nipple.

The American Cancer Society (ACS) recommends that women undergo regular mammography screening starting at age 45.² Women 45-54 should be screened annually and women 55 and over can transition to biennial screening. Women are encouraged to continue screening as long as they are in overall good health and have a life expectancy of 10 years or longer.

A number of different tests are used to look for and diagnose breast cancer, including magnetic resonance imaging (MRI), diagnostic mammogram, breast ultrasound, and breast biopsy. In some instances, suspected breast cancer can be ruled out with a diagnostic mammogram, breast ultrasound, or breast MRI. If breast cancer cannot be ruled out using those tests, a biopsy is necessary.³

The two main types of biopsies are needle and surgical biopsies. When a biopsy is performed, cells or tissue is removed from the suspicious area of the breast and studied under a microscope to determine whether cancer is present. If cancer is present, the biopsy material is also used to determine the aggressiveness of the cancer by measuring biomarkers predictive of cancer behavior, including the expression of estrogen receptors (ER), progesterone receptors (PR) and amplification of the HER2 gene. These biomarkers, combined with staging, are utilized to determine the likelihood that microscopic spread to distant organs has occurred and therefore to guide decisions on systemic therapy.

Breast Cancer Staging and Markers

I will offer opinions about breast cancer staging and markers. Breast cancers are given pre- and post-surgery staging. In general, the higher the stage of the breast cancer, the higher the likelihood that there has been systemic spread and the worse the prognosis for long-term survival. Staging is an important part of determining a patient's prognosis and best treatment options.

Breast cancer staging incorporates tumor size, the degree of lymph node involvement and the presence of gross distant metastases, and the so called TNM staging system. Other prognostic factors include, the cancer's grade, ER and PR expression, HER2 amplification, and apparent growth rate (Ki67 expression). For TNM, T represents the size of the primary tumor. T scores ranges from Tis (tumor is still in situ, that is, not invasive) to T4 (largest tumor). N represents lymph node status. N scores range from 0 (no lymph node involvement) to 3 (more than nine lymph nodes involved). M represents known metastatic disease, gross cancer already detectable in a distant site. M0 indicates it has not become evident in distant tissues. M1 indicates that it has. Generally speaking, the larger the tumor and the greater the lymph node involvement, the higher the stage and the greater the

² Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society.

³ A biopsy is the only definitive way to diagnose breast cancer.

likelihood that microscopic spread has occurred. Once the cancer has metastasized beyond the lymph nodes and grown to a size there that is detectable, it is no longer curable; this is stage IV cancer and the goals of therapy are palliative, not curative.

The cancer's grade is also evaluated. Grades range from G1 to G3. The grade of the cancer evaluates how different from a normal cell the cancer cell appears. The higher the grade, the more likely that cancer is to have spread microscopically beyond the breast.

Biomarkers are also measured and used to determine the likelihood that a woman needs systemic treatment to address microscopic spread. ER expression, PR expression, and HER2 gene amplification are the main biomarkers. ER and PR expression suggests that the cancer cells remain sensitive to and dependent upon estrogen for their survival. These cancers, in general have a better prognosis. According to the American Cancer Society, two out of every three cases of breast cancer are hormone receptor positive.

Human epidermal growth factor receptor 2 (HER2/neu or HER2) is a cell surface receptor protein that is overexpressed in 20%-25% of human breast cancers; when it is overexpressed this is a marker of dependence of that breast cancer on the HER2 pathway and of a much more aggressive behavior.

Beyond TNM stage, there are four main breast cancer biomarker subtypes: ER+/HER2-, ER-/HER2-, ER+/HER2+, and ER-/HER2+. ER+/HER2- breast cancer tends to be slower growing and less aggressive and is associated with the most favorable prognosis. ER-/HER2-, also known as triple negative breast cancer, is associated with a poorer short-term survival because there are no targeted therapies for these tumors and they tend to be inherently aggressive. While HER2+ cancers are aggressive cancers, the advent of targeted therapies, including Herceptin, have vastly improved HER2+ survival outcomes for patients diagnosed before gross distant metastases have become evidence and properly treated, these cancers are no longer associated with a very poor prognosis.

Treatment Options and Patient Attitudes

I will discuss the treatment options for breast cancer, including surgery, radiation, chemotherapy, targeted therapy, and hormonal therapy. In addition, I will discuss common sentiments breast cancer patients may have and express to me regarding treatment and survival.

For patients with advanced, stage IV, grossly metastatic breast cancer, cure is not achievable and the goal of therapy is palliation, with control of the disease and the resulting symptoms for as long as possible, balancing side effects of cancer and side effects resulting from its treatment to optimize quality of life. Early breast cancer, that is, breast cancer diagnosed before gross distant metastases have become evident, is potentially curable and the primary goal of treatment is efficacy, as measured by cure rates and survival. This is in part because if the breast cancer recurs with gross metastatic disease, patients are no longer

curable and will ultimately die of their disease. Once the cancer returns, even with existing therapies, the median five-year survival rate is approximately 16% and the 10-year survival rate is approximately 6%. Because of this, an oncologist approaches early breast cancer by assessing the risk of recurrence and, if there is a significant risk, treating very aggressively to minimize the chance that it will relapse, and to thereby provide the patient with the best chance of long term survival.

Based on my clinical practice, not surprisingly, for women who are diagnosed with early breast cancer survival is their greatest priority. Women often make treatment-related decisions that have an impact on their appearance. As an example, some women opt for prophylactic bilateral mastectomies, even without having a high risk BRCA mutation, despite the data indicating that having a prophylactic bilateral mastectomy in this setting does not increase overall survival rates, while carrying significant cosmetic sequelae. Women frequently opt for that procedure for peace of mind. Women seeking peace of mind from their treatment is consistent with the patient attitudes that I see in my practice.

Patients also choose to receive chemotherapy and/or hormonal (estrogen interdicting) therapies that have substantial side effects to increase their chances of long-term survival. Surgery and radiation therapies are localized treatments given to treat patients with early breast cancer, but they cannot address distant microscopic disease. Systemic treatments including chemotherapy, hormonal therapy and targeted HER2 directed therapies, given in conjunction with localized therapies to women with early breast cancer, are called adjuvant therapies.

Patient Counseling

I will offer testimony on patient reactions to a cancer diagnosis, discussions with patients regarding treatment and side effects, and the patient decision-making processes. Fear, shock, disbelief, sadness, and anger are all normal, common emotions for women recently diagnosed with breast cancer. Upon diagnosis, many patients think about what is important in their lives, including friends, family, and loved ones. Not surprisingly, patients have a strong desire to live, and the majority of patients are willing to take any possible treatment to maximize survival and reduce their relapse risk. When deciding upon a chemotherapy regimen, the patients' primary focus is on what regimen will optimize their survival, a very distant secondary concern is side effects.

As a medical oncologist, I meet with a patient with early breast cancer to explain her relapse risks with and without systemic adjuvant treatment, treatment options, potential side effects, and management of those side effects. I typically meet with a patient for the first time after they have their biopsy results but before surgery. Thus, when I first meet with the patient, we know the hormone receptor (ER) status of their cancer and whether it is HER2+ or HER2-. Additionally, while we do not know definitively the cancer's size, lymph node involvement, or if it has metastasized, we often generally have a good idea about the cancer's stage and systemic treatment options.

Consequently, during that first meeting, I talk with the patient about the potential treatment plan and next steps in her treatment. I often discuss survival outcomes both with and without adjuvant systemic therapy. More specifically, I tell the patient that their chance of recurrence and breast cancer related death decreases if their risk is substantial and they receive adjuvant chemotherapy. In addition to the benefits of chemotherapy, I discuss the potential side effects. And I make a recommendation for their chemotherapy, pending final results from the surgery when appropriate.

I meet with the patient again after surgery to finalize the treatment plan. After surgery, we may have revised measures of the size of the tumor, and know definitively the degree of lymph node involvement. In the adjuvant setting, during this meeting I will make my final chemotherapy recommendation and again discuss the potential benefits and risks. I will make sure the patient understands that survival is the primary goal. I will discuss with the patient that if the cancer returns systemically, her chance of survival is diminished drastically. I will make sure the patient understands the importance that we focus our efforts on minimizing her chances of breast cancer death. The vast majority of the time the patient accepts my recommended treatment plan.

It is impossible to warn a patient of all potential side effects from chemotherapy. Therefore, a clinician must decide which side effects to warn bring into the discussion. Generally speaking, clinicians warn of life-threatening side effects, side effects that occur with regularity, and side effects for which there is an effective countermeasure. In general, unless the side effect is life-threatening, clinicians do not warn of rare side effects. In addition, clinicians do not warn of side effects that have not been proven to occur. While I do warn of alopecia, I do not tell my patients that Taxotere causes permanent alopecia. When I warn of alopecia, which I do for all adjuvant chemotherapy regimens for early breast cancer, I tell patients that their hair may grow back differently. Their hair may come back thinner, be a different texture, or a different color. We also discuss cold cap countermeasures. For patients with ER+ breast cancers, I also discuss the effects of hormonal therapies on hair and hair recovery.

As an oncologist, one of my goals is to help diminish a patient's fear, while encouraging them to make appropriate treatment-related decisions.

Surgery

While surgery is often done before chemotherapy, there are times when chemotherapy is administered before surgery. This type of chemotherapy is called neoadjuvant chemotherapy. Neoadjuvant chemotherapy is typically administered to reduce the tumor size prior to surgery and to assess the response of the tumor to the treatment.

Surgery is usually the first treatment option for breast cancer patients. The surgical oncologist conducts the surgery. Depending on the size and location of the tumor, some

patients have a choice between a mastectomy and a lumpectomy. For larger tumors, lumpectomies are often not an option. In cases where the cancer is limited to one breast, some patients opt to have a prophylactic bilateral mastectomy. Studies indicate that prophylactic bilateral mastectomies do not increase overall survival rates. Yet, bilateral mastectomies include surgical risks, as well as appearance-related impacts.

If breast cancer spreads, one of the first places it is likely to go are the lymph nodes in the underarm. As such, during breast cancer surgery, a tracer is injected into the primary breast tumor. That tracer is followed to see which lymph nodes it goes to. Those lymph nodes are removed and inspected under the microscope to determine if they are cancerous. This is called a sentinel lymph node biopsy.

The extent and the involvement of the lymph nodes in breast cancer are considered to be a strong predictor of recurrence and survival. As discussed more fully below, if cancerous cells are prevalent in the lymph nodes, it is a sign that the cancer cells have spread to other organs as well, even if these sites of spread are not large enough to detect with any scans.

One of the more serious side effects of lymph node removal is lymphedema. Lymphedema is swelling in the arm or legs resulting from a blockage in the lymphatic system. In some cases, lymphedema can be severe making the affected limbs difficult to use and painful. Smoking, obesity, radiation therapy to the axilla, and diabetes increase a woman's chance of developing lymphedema following surgery. Lymphedema is a permanent side effect. Lymphedema is an example of a very significant potential side effect of treatment that women are willing to accept to ensure they are cancer free.

Before surgery, some women are tested to determine if they have genetic mutations that put them at greater risk for breast cancer. In particular, BRCA mutations put women at a greater risk for breast and ovarian cancer. Consequently, when women test positive for BRCA mutations, often times they will opt for a prophylactic oophorectomy (ovary removal) to reduce the risk developing additional cancer. These women will also often opt for prophylactic mastectomies.

Women who have had a mastectomy will have the choice of reconstructive surgery. Reconstructive surgery is performed by a plastic surgeon.

Radiation Therapy

Radiation oncologists administer radiation therapy. Radiation therapy is a highly effective way to kill cancer cells in a given location. It uses high-energy beams to damage a cell's DNA. Radiation, like chemotherapy, can also damage normal cells in its path. Radiation is always recommended for patients who have lumpectomies. For women who have the option to have a lumpectomy, overall survival rates are equivalent between having a mastectomy and having a lumpectomy plus radiation. In addition, for more advanced cancers, radiation is recommended for women who have mastectomies. Radiation is given

to reduce the risk of local recurrence of cancer. Potential side effects of radiation therapy include armpit dysfunction, chest pain, fatigue, heart problems, lowered white blood cell counts, and lung problems. In addition, radiation can complicate wound healing. It can also alter the skin. A potential side effect of radiation is that reconstructive surgery cannot be done due to poor wound healing or alterations to the skin.

Chemotherapy

Another component of breast cancer treatment is chemotherapy. Chemotherapy medicine cannot be lawfully obtained in the United States without a doctor's prescription. Medical oncologists create chemotherapy plans for the patient. Chemotherapy is given to kill cancer cells that have migrated to distant parts of the body and, although not yet detectable by scanning, will result in the development of metastatic disease in the future. Chemotherapy reduces the risk that this will occur. The significant proportion of early breast cancer patients need adjuvant chemotherapy to optimize their survival chances. Chemotherapy can be given in a neoadjuvant, adjuvant, or metastatic setting. For purposes of this report, I will focus on chemotherapy in an adjuvant setting.

Chemotherapy is treatment by means of anti-cancer drugs that kill cancer cells. Modern chemotherapy is given including at least two or three different chemotherapy drugs. This is because a multi-drug regimen has greater efficacy than monotherapy.

The primary goal of chemotherapy is to improve survival rates. In general, I would not recommend that a patient take a less effective chemotherapy regimen due to potential appearance-related side effects.

Chemotherapy regimens to treat breast cancer have evolved over time. This evolution is based on the availability of new drugs that clinical trials have shown to provide greater efficacy with an acceptable side effect profile. Currently, the most effective adjuvant chemotherapy regimens for early breast cancer are taxane-containing regimens.

Taxanes are uniquely effective in treating breast cancer due to their mechanism of action. The principal mechanism of action for the taxane class of drugs is the disruption of microtubule function. Taxanes are mitotic spindle poisons (a poison that disrupts cell division) and work by inhibiting microtubules. In normal cell division, microtubules pull chromosomes to each side of a cell, which allows the cell to copy itself and divide. Taxanes inhibit this process and essentially prevent the cell from being able to divide, which kills the cancer cell.

The older non-taxane containing regimens, including FEC, CMF, and AC have lower overall survival rates than taxane-containing regimens. Consequently, I would not recommend that a woman take a non-taxane containing chemotherapy regimen because her overall survival rate would diminish. The older chemotherapy regimens are not reasonable alternatives for taxane-containing regimens.

Recently, tests such as the Mammaprint and Oncotype DX tests have been used to help assess whether very low risk breast cancer patients may benefit from adjuvant chemotherapy. Those tests are only used in a subset of breast cancer patients. Those tests are not a substitute for an oncologist's clinical judgment.

Survival Rates for Breast Cancer

I will discuss survival rates for breast cancer, including the impact that various chemotherapy regimens have on improving overall survival rates. Survival rates are used to understand a patient's prognosis, compare different treatment approaches, and develop an appropriate treatment plan. Survival rates are often measured in terms of a five-year and ten-year survival rate.

Until 1995, breast cancer death rates had remained nearly unchanged for 40 years. Over time, treatment options for and earlier detection of breast cancer have led to increased survival rates.⁴

Today, however, 5-year and 10-year survival rates for invasive breast cancer are 90% and 83%.⁵

The Development of Chemotherapy

I will discuss the evolution of chemotherapy. Before the advent of chemotherapy, the only treatment options a woman had for breast cancer were disfiguring surgeries and radiation. Eventually, oncologists realized that no matter how extreme the surgery, the overall survival rates were unchanged. This is because even radical surgeries did not rid the woman's body of micrometastases. Those micrometastases resulted in distant cancer recurrence and death.

This understanding resulted in the use of drugs in conjunction with (or "adjuvant to") surgery or radiation treatments to prevent micrometastases. To combat micrometastases, oncologists developed chemotherapy and chemotherapy regimens. The application of chemotherapy drugs to the treatment of early breast cancer was associated with an improvement in overall survival. This approach continues to be widely applied in the treatment of early breast cancer.

Chemotherapy has improved over time. More specifically, new chemotherapy drugs have been developed and new chemotherapy regimens have been studied, which have improved overall survival rates. As chemotherapy regimens evolve, the newest generation of chemotherapy regimens become the "standard of care." This is because they offer the best

⁴ Data Sources: National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2016.

⁵ Cancer Stat Fact: Female Breast Cancer, <https://seer.cancer.gov/statfacts/html/breast.html>.

survival rates and offer the patient the optimal chance for survival.

In patients with early breast cancer, taxanes improved survival rates compared to chemotherapy regimens that do not include taxanes. The current standard of care for adjuvant chemotherapy requires that the regimen contain a taxane, except in the rare circumstance of patients with a serious pre-existing neuropathy or a known taxane allergy. In general, patients should not be given outdated chemotherapy regimens, including: AC, FEC, FAC, CAF, CEF, CMF, and EC. Those regimens have lower survival rates, compared to taxane-containing regimens. In general, clinicians do not recommend those regimens to patients. I will discuss the difference in survival rates between the older regimens and taxane-containing regimens.

Taxotere (docetaxel)

I will discuss the development of taxanes. In the 1950s, the National Cancer Institute (NCI)⁶ created the Cancer Chemotherapy National Service Center (CCNS). CCNS's goal was to find new anti-cancer compounds. As part of that process, they analyzed thousands of compounds and plants to determine if they had anti-cancer properties. CCNS found that the bark from the Pacific Yew tree had highly cytotoxic properties and a unique mechanism of action. The problem is that the Pacific Yew tree was extremely slow-growing and in limited supply.

To collect the bark, the yew tree had to be killed. It required 100 Pacific Yew trees to produce a single gram of purified Taxol. In other words, 360,000 Pacific Yew trees were required to produce enough Taxol to treat 20,000 patients.

As Jordan Goodman writes in *The Story of Taxol*, "Whatever the true population of *taxus brevifolia* in the Pacific Northwest was, it was finite and depleting. Cancer was not."

Due in part to environmental concerns regarding the impact on the forest and the possibility of using up all the Yew trees, news stories began appearing, and the public became more aware of the existence of Taxol. To overcome this supply and demand problem, the cytotoxic naturally occurring molecule needed to be synthesized. Researchers were able to create a synthetic molecule. That initial synthesized molecule was the drug that became known as Taxol.

But researchers continued to work on other synthesized molecules. One researcher was Dr. Pierre Portier. In 1980, Dr. Portier began working on a process to semi-synthesize Taxol and Taxol-derivatives with improved anti-cancer activity. His team focused on the common yew due to its abundance near the Center for National Scientific Research (CNSR) in France. From the needles of the common yew tree, Portier's team isolated a

⁶ The National Cancer Institute (NCI) is part of the National Institute of Health (NIH) and 1 of 11 agencies that make up the Department of Health and Human Services (HHS).

precursor taxane molecule. Portier entered a collaborative agreement with Rhone-Poulenc to expedite research and development. The semi-synthesis process developed by Portier and his team ended with the drug that became known as Taxotere.

During in vivo testing, the Taxotere molecule showed greater anti-cancer activity than Taxol.

Phase I clinical trials for Taxotere began in 1990, which addressed dosing and administration schedules. Phase II studies began in 1992, and by 1994, Taxotere was in Phase III clinical trials for multiple indications. In 1996, the FDA approved Taxotere for treatment of metastatic breast cancer with progression or relapse after previous anthracycline-based chemotherapy. In 1998, the FDA approved Taxotere for treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy. Then, in 2004, the FDA approved Taxotere for adjuvant treatment of operable node-positive breast cancer in combination with doxorubicin and cyclophosphamide.

In general, Taxotere is not given as a monotherapy in the adjuvant treatment of early breast cancer. It is given as part of a multi-drug chemotherapy regimen. Taxotere is more effective when used as part of a multi-drug chemotherapy regimen. When used in the adjuvant treatment for breast cancer, Taxotere is generally administered in a 75 mg/m² dose that is generally given every 21 days in 4-6 cycles in combination with other chemotherapy drugs.

While the FDA approves drugs for very specific indications, drugs, including Taxotere, are frequently used off label.

Taxotere is approved to treat breast cancer, non-small cell lung cancer, gastric adenocarcinoma, squamous cell head and neck cancers, and hormone refractory prostate cancer. Taxol does not share the same approval indications as Taxotere.

Taxotere is a life-saving drug. It is included on the WHO's list of essential medicines, which is defined as "the most efficacious, safe, and cost-effective medicines for priority conditions."

Taxotere (Docetaxel) and Taxol (Paclitaxel) Are Not Interchangeable

While Taxol and Taxotere are both taxanes, they are not the same drug. They have different drug profiles, different toxicities, and are prescribed for different indications. Taxotere-containing regimens offer benefits over Taxol-containing regimens.

Chemotherapy regimens are based on clinical trials. As such, one chemotherapy drug cannot be swapped out for another chemotherapy drug in a regimen. In other words, Taxol cannot be substituted for Taxotere in Taxotere-containing regimens and vice versa without clinical trials demonstrating equivalent efficacy in that particular setting

The established regimens for Taxotere and Taxol may contain different drugs. Notably, for both HER2+ and HER2- breast cancer, patients can avoid Adriamycin and other anthracyclines by taking a Taxotere combination regimen. In contrast, for both HER2+ and HER2- breast cancers, all of the studied and established Taxol-containing regimens must include anthracyclines as part of their regimen. Adriamycin can cause irreversible heart damage and fatal leukemia.⁷ Patients can avoid those potentially lethal side effects by taking Taxotere regimens and not taking Adriamycin.

If Adriamycin is included in a regimen, Taxotere can be administered concurrently with Adriamycin. Taxol, however, cannot be administered concurrently with Adriamycin because the co-administration increases cardiotoxicity. Because Taxol cannot be administered until after all Adriamycin cycles have been completed, the patient is at risk of not being able to receive Taxol if cardiac or other serious complications occur during the Adriamycin cycles.

In addition, the side effect profiles of Taxol and Taxotere are different. Both Taxotere and Taxol are microtubule targeting chemotherapy medication. But the risk of severe neuropathy is much lower with Taxotere than Taxol. Neuropathy is a side effect of taxane chemotherapy. Neuropathy can be permanent. It is a quality of life concern. Because Taxol has higher rates of neuropathy than Taxotere, diabetics and pre-diabetics are at increased risk of neuropathy when treated with Taxol.

Taxol and Taxotere-containing regimens are also given on different dosing schedules. More specifically, Taxol is usually given weekly. Whereas, Taxotere is given once every three weeks. Chemotherapy given every three weeks has a number of medical and quality of life advantages. As far as quality of life, many patients find that only having chemotherapy once every three weeks is more convenient. Medically, one problem with weekly therapy is that patients receive more corticosteroids than when treated once every three weeks. Corticosteroids are associated with numerous toxicities including insomnia, allergic reactions, delirium, immune suppression and infections, weakness, psychosis, stomach ulcers and gastritis, elevated blood pressure/blood sugar, and osteoporosis.

NCCN Guidelines

The National Comprehensive Cancer Network (NCCN) is an alliance of 27 cancer centers throughout the United States. The NCCN issues recommendations for adjuvant breast cancer chemotherapy regimens based on breast cancer tumor markers. The guidelines have changed overtime as new clinical trial data becomes available. The guidelines set forth “preferred adjuvant regimens” and “other adjuvant regimens.” Taxane containing

⁷ See Pinder, M., et al. Congestive Heart Failure in Older Women Treated With Adjuvant Anthracycline Chemotherapy for Breast Cancer. *J Clin Oncol* 2007;25(25):3808-3815; Diamandidou, E., et al. Treatment-Related Leukemia in Breast Cancer Patients Treated with FEC Combination Adjuvant Chemotherapy. 1996;14(10):2722-2730.

regimens are listed under the preferred regimens. This is because they are more effective than the “other” regimens. While numerous regimens are listed in the NCCN guidelines, many of those regimens are included for insurance coverage purposes for special patient populations. Those regimens are frequently not the standard of care. Taxane-containing regimens are the standard of care for adjuvant breast cancer chemotherapy regimens for most patients.

Chemotherapy Regimens for HER2- Breast Cancer

I will discuss chemotherapy regimens used to treat HER2- breast cancer. My preferred chemotherapy regimen for HER2- breast cancer is TC (Taxotere, Cyclophosphamide). Some doctors use the AC-T (Adriamycin and Cyclophosphamide followed by Taxol) regimen for HER2- breast cancer. Others use TAC (Taxotere, Adriamycin and Cytoxan) or AC-T using Taxotere for the “T.” While all of these regimens have similar efficacy, some physicians believe that the Adriamycin containing regimens have slightly higher efficacy. These are all within the standard of care. Adriamycin brings with it the risk of fatal leukemia and heart concerns.⁸ The risk of cardiac toxicity is increased in patients of advanced age or those with a prior history of heart disease.

Heart damage caused by Adriamycin may not appear until decades after treatment has ended. In fact, when following the cohort of women who have been given Adriamycin as they age, they have higher rates of heart failure than women who had not been given Adriamycin. This is because Adriamycin damages the heart. Adriamycin is often called the “red devil” or “red death” because of its harsh side effects and its color. The risk of cardiac toxicity and leukemia are lower with the TC regimen.

Additionally, women who are obese, pre-diabetic, diabetic, or have heart issues may be suboptimal candidates for Taxol-containing regimens. This is because Taxol-containing regimens, and the attendant increases in steroid exposure with the requisite more frequent taxane administration when Taxol is used rather than Taxotere, put them at risk of neuropathy and cardiac toxicity. As such, for women who are obese, pre-diabetic, diabetic, or have heart issues, there are reasons to consider using TC.

If a patient decides to receive an Adriamycin-containing regimen, there are advantages of TAC over AC-T. First, Taxol has a higher risk of neuropathy than Taxotere. A patient’s risk of neuropathy is reduced with the TAC regimen. Further, for patients that are diabetic and already at an increased risk of neuropathy, Taxol has increased risks.

Second, TAC is administered every three weeks, whereas the Taxol in AC-T is given weekly. The TAC regimen is more convenient for the patient. Additionally, by administering chemotherapy every three weeks instead of weekly, the patient is able to

⁸ Barrett-Lee, P.J., et al. Expert Opinion on the Use of Anthracyclines in Patients with Advanced Breast Cancer at Cardiac Risk, *Ann Oncol.* 2009;20:816-827.

avoid additional steroids. Avoiding additional steroids enables the patient to avoid unnecessary side effects and discomfort, including sleep disturbances, increased sugar levels, weight gain, and immune complications. Finally, Taxol and Adriamycin cannot be given at the same time. Thus, the patient receives Adriamycin and Cyclophosphamide cycles first followed by Taxol. If the patient has cardiac complications, that can impact administering the remainder of the chemotherapy regimen.

When Adriamycin-containing regimens are given, oncologists must order cardiac tests on the patient before administering the regimen. If the patient's ejection fraction is reduced, it may be necessary to discontinue Adriamycin. Moreover, other factors should be taken into consideration in determining whether a patient should be given Adriamycin, including if the patient is obese, has hypertension, or has a family history of heart disease. Further, the risk of cardiac toxicity from Adriamycin is dose-dependent. Stated differently, the more Adriamycin a person is given, the greater the risk they will develop left ventricular failure.

Chemotherapy Regimens for HER2+ Breast Cancer

I will discuss chemotherapy regimens used to treat HER2+ breast cancer. Herceptin (trastuzumab) is part of the recommended regimen for HER2+ breast cancer because it blocks the ability of the cancer cells to receive chemical signals that tell the cancer cells to grow and become more sensitive to chemotherapy

My preferred treatment regimen for early HER2+ breast cancer is TCH (Taxotere, Carboplatin, Herceptin) or TCH+P.⁹ While AC-TH is a treatment regimen for HER2+ breast cancers, that regimen has increased risks that are not present with the TCH regimen. In particular, Adriamycin must be given with the Taxol containing regimen. As such, the patient is at risk of cardiac toxicity and leukemia. Additionally, the risk of cardiac toxicity increases when both Herceptin and Adriamycin are administered. To decrease that risk somewhat, Herceptin and Adriamycin must be given sequentially, instead of at the same time. As such, the administration of Herceptin is delayed. That is problematic because the Herceptin is what targets the HER2+ cancer and makes chemotherapy more effective. Further, if the patient has cardiac complications that can impact administering the remainder of the chemotherapy regimen. Those risks are reduced with the Taxotere containing regimen. In addition, Taxotere and Herceptin have been shown to work together synergistically in killing HER2 positive breast cancer cells. In contrast, Taxol and Herceptin are additive but not synergistic. Finally, randomized trials demonstrating the efficacy of Herceptin coupled with anthracycline free Taxol based chemotherapy have not been published.

⁹ See Slamon, D., et al. Adjuvant Trastuzumab in HER2-Positive Breast Cancer. N Engl J Med. 2011;365(14):1273-83.

Hormone Positive Breast Cancer

Women who have early hormone receptor positive breast cancer and require systemic therapy following local treatments are given either the selective estrogen receptor modulator (SERM) Tamoxifen or aromatase inhibitors. Currently, the recommendation is that women use those medications for 5 to 10 years.

Hormone receptor positive cancers require estrogen to grow. Tamoxifen interferes with estrogen's ability to support the growth of breast cancer cells. Aromatase inhibitors block the activity of the enzyme aromatase (used to make estrogen) and lower estrogen levels in postmenopausal women. If aromatase inhibitors are given to premenopausal women, they are used in combination with a drug that suppresses ovarian function and establishes essentially a postmenopausal state

Both Tamoxifen and aromatase inhibitors reduce the estrogenic stimulation to ER+ breast cancer. Both of these hormonal therapy approaches can cause hair thinning and loss as alopecia.¹⁰ In addition, the labels for Tamoxifen and aromatase inhibitors warn of alopecia.¹¹ In my own practice, I see alopecia caused by Tamoxifen and aromatase inhibitors very frequently. The hair loss seen with Tamoxifen and aromatase inhibitors can mimic the alopecia seen with androgenetic alopecia. It can also appear in a more diffuse pattern.

Breast cancer patients who are treated with taxane-containing chemotherapy regimens will generally undergo anagen effluvium and will lose all of their hair. Then, after they complete their chemotherapy regimen, women with ER+ or PR+ cancers will begin taking either Tamoxifen or an aromatase inhibitor. Because those drugs can cause alopecia, those drugs can be responsible for a woman's hair not regrowing.

In addition to persistent alopecia, Tamoxifen and aromatase inhibitors have other side effects. Tamoxifen increases a woman's risk of endometrial cancer. Aromatase inhibitors cause loss in bone density. Other side effects of Tamoxifen and aromatase inhibitors include joint pain, nausea, hot flashes, fatigue, mood swings, headache, depression, chest pain, weakness, weight gain, and loss of libido. These side effects can significantly diminish a woman's quality of life. Yet, the vast majority of women are willing to endure the side effects to improve their chances of survival.

¹⁰ Palamaras, I. Letter to Editor, Permanent Chemotherapy-Induced Alopecia: A Review, *J Am Acad Dermatol.* 2011 Mar;64(3):604-606; Park, J., et. al. Pattern Alopecia During Hormonal Anticancer Therapy in Patients with Breast Cancer. *Ann of Dermatol.* 2014;26(6):743-46; Fonia, A., et al. Permanent Alopecia in Patients with Breast Cancer After Taxane Chemotherapy and Adjuvant Hormonal Therapy: Clinicopathologic Findings in a Cohort of 10 Patients. *J. Am Acad Dermatol.* 2017;76(5):948-57.

¹¹ Aromatase inhibitors such as Letrozole, Raloxifene, Toremifene, Anastrozole, and Exemestane all warn of the risk of alopecia on their labels.

While hormonal therapies are effective, in ER positive breast cancer, they do not replace chemotherapy for patients with a significant risk of relapse. In these women, the hormonal therapies are used in addition to, rather than instead of, chemotherapy.

Side Effects of Chemotherapy Drugs

I will discuss side effects of chemotherapy drugs, how clinicians weigh side effects, and how and what side effects are communicated to the patient. All chemotherapeutic drugs have side effects, including very serious side effects, such as death. Well-known side effects include nerve or muscle problems, infection/neutropenia (low white blood counts), fatigue, nausea, alopecia, diarrhea, loss of fertility which can be permanent, heart damage, bladder or kidney problems, weight changes, mood changes, constipation, and skin and nail changes. Side effects vary greatly from person to person. Additionally, the severity of side effects varies from person to person. Permanent side effects can include damage to the heart, lungs, kidneys, or reproductive organs, or a second cancer.

As a clinician, when warning about potential side effects of chemotherapy drugs, I warn about common side effects and side effects that are life threatening. It is impossible to warn of all potential side effects. Additionally, when warning patients about side effects it is impossible to tell a patient which side effects that patient will have out of the wide spectrum of potential side effects.

Alopecia Generally

I will offer opinions regarding types of alopecia and causes of alopecia. There are many types and causes of alopecia. As women age, their risk of alopecia increases.¹² Accordingly, post-menopausal women have a greater risk of alopecia.¹³

The most prevalent form of alopecia seen in women is androgenic alopecia, which is also called female-pattern baldness.¹⁴ It is a non-scarring form of alopecia. This type of alopecia resembles male-pattern baldness. The hair loss typically occurs in the crown area, although it can occur over the entire scalp. The severity of hair loss caused by androgenetic alopecia can vary from minimal to complete baldness. Approximately, 50-60% of women have some degree of androgenetic alopecia by age 50. In addition to age, androgenetic alopecia can be caused by a hormone imbalance, or being post-menopausal, among other causes.

¹² See Ali, I., et al., Physiological Changes in Scalp, Facial, and Body Hair After Menopause: A Cross-Sectional Population-Based Study of Subjective Changes, *British J Dermatol.* 2011;164.3:508-09.

¹³ See Ali, I., et al., Physiological Changes in Scalp, Facial, and Body Hair After Menopause: A Cross-Sectional Population-Based Study of Subjective Changes, *British J Dermatol.* 2011;164.3:508-09.

¹⁴ Shapiro, J. Hair Loss in Women. *N Engl J Med.* 2007;357:1620-1630.

In addition, other common causes of alopecia include but are not limited to: medicines,¹⁵ stress, surgery, illness, hormone imbalances, obesity, heart disease, Metabolic Syndrome,¹⁶ thyroid conditions, vitamin deficiencies,¹⁷ iron deficiencies,¹⁸ hair care practices,¹⁹ organ problems, and autoimmune diseases. Determining the cause of alopecia can be very difficult because the cause of alopecia can be multifactorial. In addition, when considering the cause of alopecia one must consider a woman's family history, medical history, current health, medications, blood tests, nutritional issues, genetics, and organ malfunction. Further, hair loss can occur over time and be cumulative. Many women will not recognize the extent of the hair loss until after normal chemotherapy-related changes to hair, including thinning. Many of the established risk factors for alopecia overlap with the demographics of women who have been diagnosed with breast cancer.

Alopecia After Chemotherapy

I will offer opinions regarding whether chemotherapy drugs may cause alopecia. Alopecia is a common side effect of most chemotherapy drugs. This type of alopecia is called anagen effluvium. Hair loss occurs because chemotherapy targets rapidly dividing cells, including cells in hair follicles.

After recovering from chemotherapy, approximately, 65% of people who have undergone chemotherapy experience a change from their previous hair, including differences in texture, thickness, or color.²⁰ This is a widely known side effect of chemotherapy.

Cases of ongoing alopecia have been reported with Adriamycin,²¹ Carboplatin,²²

¹⁵ Shapiro, J. Hair Loss in Women. N Engl J Med. 2007;357:1620-1630; Goldberg, L. Postmenopausal Alopecia (Hair Loss), chp. 11 Essentials of Menopause Management. Pal and Sayegh ed. Springer; 2017. ISBN 978-3-319-42449-1.

¹⁶ Roth, MM, et al. Gynecologic and Andrologic Dermatology and the Metabolic Syndrome. Clin Dermatol. 2018;36(1):72-80; Uzuncakmak, TK, et al. Cutaneous Manifestations of Obesity and the Metabolic Syndrome. Clin Dermatol. 2018;36(1):81-88; Lie, C, et al. Alopecia and the Metabolic Syndrome. Clin Dermatol. 2018;36(1):54-61; El Sayad, MH, et al., Association of Metabolic Syndrome With Female Pattern Hair Loss in Women: A Case-Control Study, Int J Dermatol. 2016;55(10):1131-7.

¹⁷ See, e.g., Lie, C, et al. Alopecia and the Metabolic Syndrome. Clin Dermatol. 2018;36(1):54-61.

¹⁸ Shapiro, J. Hair Loss in Women. N Engl J Med. 2007;357:1620-1630.

¹⁹ Shapiro, J. Hair Loss in Women. N Engl J Med. 2007;357:1620-1630.

²⁰ Batchelor, D. Hair and Cancer Chemo: Consequences and Nursing Care—A Literature Study. 2001;10(3):147-63; Beisecker, A., et al. Side Effects of Adjuvant Chemotherapy: Perceptions of Node-Negative Breast Cancer Patients. Psychooncology. 1997;6(2):85-93.

²¹ Masidonski P, et al. Permanent Alopecia in Women Being Treated for Breast Cancer. Clin J Oncol Nurs. 2009;13(1):13-4; Crown, J., Incidence of Permanent Alopecia Following Adjuvant Chemotherapy in Women w/ Early Stage Breast Cancer. J Clin Oncol. 2017;35(15):Supp. Abstract e21576; Yeager C., et al. Treatment of Chemotherapy-Induced Alopecia, Dermatologic Therapy. 2011;24(4):432-442; Jung, MY, et al. A Clinical Study of Chemotherapy-Induced Permanent Alopecia. 51(12) Korean J Dermatol. 2013;51(12):933-938.

²² De Jonge, ME, et al. Relationship Between Irreversible Alopecia and Exposure to Cyclophosphamide, Thiotepa and Carboplatin (CTC) in High-Dose Chemotherapy. Bone Marrow Transplantation. 2002;30:593-597.

Cisplatin,²³ Taxol,²⁴ Epirubicin, Etoposide, 5-Fluorouracil,²⁵ Busulfan,²⁶ Gemcitabine, Idarubicin, Ifosfamide, Melphalan,²⁷ Thiotepa,²⁸ and Cyclophosphamide.²⁹ Persistent alopecia after chemotherapy is a potential side effect of chemotherapy regimens. Even so, there is no significant evidence that Taxotere when used as a monotherapy results in permanent alopecia as a cause.

Because Taxotere for early breast cancer is given as part of a multi-drug regimen and not a single agent, it is impossible to conclude that Taxotere causes permanent alopecia. Taxotere containing regimens can include Adriamycin, Herceptin, Carboplatin, and cyclophosphamide. For patients who were given a Taxotere containing regimen and have alopecia after the completion of chemotherapy, their alopecia could have been caused by Adriamycin, Carboplatin, or cyclophosphamide.

In addition, in cases of hormone positive early breast cancer, women are given either Tamoxifen or aromatase inhibitors, which are also known to carry a risk of alopecia. In those situations, any alopecia could be caused by Tamoxifen or aromatase inhibitors.

²³ Miteav, M, et al. Permanent Alopecia After Systemic Chemotherapy: A Clinicopathological Study of 10 Cases, *Am J Dermatopathol.* 2011;33(4):345-350.

²⁴ Prevezas, C., et al. Irreversible and Severe Alopecia Following Docetaxel and Paclitaxel Cytotoxic Therapy for Breast Cancer. *Brit J Derm.* 2009;160(4):883-885; Palamaras, I. Letter to Editor, Permanent Chemotherapy-Induced Alopecia: A Review, *J Am Acad Dermatol.* 2011 Mar;64(3):604-606; Miteav, M, et al. Permanent Alopecia After Systemic Chemotherapy: A Clinicopathological Study of 10 Cases, *Am J Dermatopathol.* 2011;33(4):345-350; Crown, J., Incidence of Permanent Alopecia Following Adjuvant Chemotherapy in Women w/ Early Stage Breast Cancer. *J Clin Oncol.* 2017;35(15):Supp. Abstract e21576; Yeager C., et al. Treatment of Chemotherapy-Induced Alopecia, *Dermatologic Therapy.* 2011;24(4):432-442; Yang, X, et al. Treatment of Permanent Chemotherapy-Induced Alopecia with Low Dose Oral Minoxidil. *Australas J Dermatol.* 2015;57(4):e130-e132; Jung, MY, et al. A Clinical Study of Chemotherapy-Induced Permanent Alopecia. 51(12) *Korean J Dermatol.* 2013;51(12):933-938.

²⁵ Beisecker, A., et al. Side Effects of Adjuvant Chemotherapy: Perceptions of Node-Negative Breast Cancer Patients. *Psychooncology.* 1997;6(2):85-93; Berglund, G., et al. Late Effects of Adjuvant Chemotherapy and Postoperative Radiotherapy on Quality of Life Among Breast Cancer Patients. *Eur J Cancer.* 1991;27(9):1075-81; Jung, MY, et al. A Clinical Study of Chemotherapy-Induced Permanent Alopecia. 51(12) *Korean J Dermatol.* 2013;51(12):933-938.

²⁶ Tosti, A., et al. Permanent Alopecia after Busulfan Chemotherapy. *Br J of Dermatol.* 2005;152(5):1056-8.

²⁷ Yang, X, et al. Treatment of Permanent Chemotherapy-Induced Alopecia with Low Dose Oral Minoxidil. *Australas J Dermatol.* 2015;57(4):e130-e132.

²⁸ M.E. de Jonge et al., Relationship b/w Irreversible Alopecia and Exposure to Cyclophosphamide, Thiotepa and Carboplatin (CTC) in High-Dose Chemotherapy; Relationship Between Irreversible Alopecia and Exposure to Cyclophosphamide, Thiotepa, and Carboplatin in High-Dose Chemotherapy, 30(9) *Bone Marrow Transplantation* 593-597 (2002).

²⁹ De Jonge, ME, et al. Relationship Between Irreversible Alopecia and Exposure to Cyclophosphamide, Thiotepa and Carboplatin (CTC) in High-Dose Chemotherapy. *Bone Marrow Transplantation.* 2002;30:593-597; Masidonski, P., et al. Permanent Alopecia in Women Being Treated for Breast Cancer, *Clin J Oncol Nurs.* 2009;13(1):13-14; Yeager C., et al. Treatment of Chemotherapy-Induced Alopecia, *Dermatologic Therapy.* 2011;24(4):432-442; Berglund, G., et al. Late Effects of Adjuvant Chemotherapy and Postoperative Radiotherapy on Quality of Life Among Breast Cancer Patients. *Eur J Cancer.* 1991;27(9):1075-81; Jung, MY, et al. A Clinical Study of Chemotherapy-Induced Permanent Alopecia. 51(12) *Korean J Dermatol.* 2013;51(12):933-938.

Further, as noted earlier, there are many other causes of hair loss, including chemotherapy induced menopause. Likewise, chemotherapy can speed up the aging process and age-related hair loss. More specifically, chemotherapy can alter a woman's hormonal status, resulting in age-related hair loss. In addition, stress and surgery are known causes of alopecia.

Moreover, calling alopecia after chemotherapy “permanent,” is inaccurate because there are case reports that persistent alopecia after chemotherapy is treatable or self-limited, and the hair will regrow.³⁰

While attributing alopecia to a given chemotherapy drug can generally be quite challenging or impossible, in my clinical experience, persistent alopecia long after chemotherapy is rare. In over 30 years of treating several thousand women with breast cancer, I have observed only 4 or 5 cases of prolonged alopecia that may have been caused by chemotherapy.

Defining alopecia as permanent or irreversible based on the time since chemotherapy is inherently unreliable. As used in the adverse event reports and clinical studies, alopecia is recorded or reported as an unwanted side effect. This is why the word “ongoing” is used to describe alopecia. Alopecia in the sense of being “permanent” or “irreversible” would require a medical diagnosis made by a clinician. Clinically-speaking, “permanent” or “irreversible” alopecia is a type of scarring alopecia where the hair follicle is no longer able to produce hair. Adverse event reports or clinical study data cannot be appropriately characterized as cases of “permanent” or “irreversible” alopecia, let alone connected to chemotherapy at the exclusion of other causes, without such clinical evaluation.³¹

Alopecia after chemotherapy has not been consistently defined in the literature. Additionally, the literature discussing alopecia after chemotherapy contains significant limitations. Ordinarily, the patients seemingly were exposed to multiple pre-existing, breast-cancer-related, and breast-cancer-treatment-related risk factors for hair loss. Retrospective studies introduce biases or confounding factors undermining any reliable conclusions. The reported pathology findings are not described consistently.

Moreover, women cannot avoid the potential risk of persistent alopecia by avoiding a Taxotere-containing regimen. The only other regimens available with similar efficacy are Taxol-containing regimens. Yet, Taxol has been associated with alopecia after the conclusion of chemotherapy. Further, in Taxol-containing regimens, patients are given Adriamycin and cyclophosphamide—both of which have been associated with alopecia after the completion of chemotherapy. This would also be true with respect to the CMF

³⁰ Yang, X, et al. Treatment of Permanent Chemotherapy-Induced Alopecia with Low Dose Oral Minoxidil. *Australas J Dermatol*. 2015;57(4):e130-e132.

³¹ Sibaud, V., et al. Dermatological Adverse Events with Taxane Chemotherapy. *Eur J Dermatol*. 2016;26(5):427-443.

chemotherapy regimen, which, while inferior in terms of efficacy to taxane based regimens, has been advocated by some as a cost-saving approach.

Even if alopecia after the completion of chemotherapy can occur with Taxotere-containing regimens, there is no reliable evidence that the incidence of alopecia after chemotherapy is any greater than that seen with Taxol-containing regimens.

Contrary to plaintiffs' experts' opinions, which cite only a small number of publications, including abstracts, of such reports, reports of alopecia after chemotherapy are not only consistently described with Taxotere, but are common with other chemotherapies.³²

Even where there are more reports in the literature of alopecia after one chemotherapy versus another, this is not level one evidence of a greater association because case reports are not prospective, they are not controlled, you do not know the differences in the patients treated with the medicines, and you do not know the number of patients treated with the medicine overall. For example, a given adverse event may be more common with medicine x over medicine y but only because so many more patients take medicine x, or because, as we believe with third generation chemotherapies, patients survive to live long enough and experience the event.

As an oncologist, even if alopecia after chemotherapy occurs with Taxotere-containing regimens, I would still usually recommend to women that they use Taxotere-containing regimens over Taxol-containing regimens. This is particularly true in patients with HER2 positive early breast cancer, where TCH avoids the need for anthracyclines that have serious risks with Adriamycin, and ER+ breast cancers, in which the data supporting

³² See Alkeraye, S., et al. Persistent Alopecia Induced by Vismodegib. *J Am Acad Dermatol.* 2015;72(5 Supp.):AB189; Baker, BW, et al. Busulphan/Cyclophosphamide Conditioning for Bone Marrow Transplantation May Lead to Failure of Hair Regrowth. *Bone Marrow Transplantation.* 1991; 7(1):43-47; Beisecker, A., et al. Side Effects of Adjuvant Chemotherapy: Perceptions of Node-Negative Breast Cancer Patients. *Psychooncology.* 1997;6(2):85-93; Berglund, G., et al. Late Effects of Adjuvant Chemotherapy and Postoperative Radiotherapy on Quality of Life Among Breast Cancer Patients. *Eur J Cancer.* 1991;27(9):1075-81; Bresters, D., et al. Permanent Diffuse Alopecia After Haematopoietic Stem Cell Transplantation in Childhood. *Bone Marrow Transplantation.* 2017;52(7):984-988; Choi, M. Clinical Characteristics of Chemotherapy-Induced Alopecia in Childhood. *J Am Acad Dermatol.* 2014;70(3):499-505; Crown, J., Incidence of Permanent Alopecia Following Adjuvant Chemotherapy in Women w/ Early Stage Breast Cancer. *J Clin Oncol.* 2017;35(15):Supp. Abstract e21576; De Jonge, ME, et al. Relationship Between Irreversible Alopecia and Exposure to Cyclophosphamide, Thiotepa and Carboplatin (CTC) in High-Dose Chemotherapy. *Bone Marrow Transplantation.* 2002;30:593-597; Jäger, E., et al. Combination of 5-Fluorouracil, Adriamycin, Ifosfamide and Cisplatin in Metastatic Adult Soft Tissue Sarcoma: Results of a Phase II Study. *Oncol.* 1996;53(1):58-63; Jung, MY, et al. A Clinical Study of Chemotherapy-Induced Permanent Alopecia. 51(12) *Korean J Dermatol.* 2013;51(12):933-938; Ljungman, P. Busulfan Concentration in Relation to Permanent Alopecia in Recipients of Bone Marrow Transplants. *Bone Marrow Transplant.* 1995; 15(6):869-871; Motl, S., et al. Recurring Chemotherapy-Associated Alopecia Areata: Case Report and Literature Review. *Pharmacotherapy.* 2003;23(1):104-108; Schrama, JG, et al. Phase II Study of a Multi-course High-dose Chemotherapy Regimen Incorporating Cyclophosphamide, Thiotepa, and Carboplatin in Stage IV Breast Cancer, *Bone Marrow Transplantation.* 2001; 28:173-180.

anthracycline use are particularly suspect. Even if there is a risk of alopecia, that potential risk is far outweighed by the detrimental and potentially fatal risks of cardiac toxicity and leukemia.

Cooling Caps

Cooling caps were not approved by the FDA at the time Ms. Earnest, Ms. Durden, and Ms. Francis underwent chemotherapy. There is the risk of scalp metastases when a patient uses a cooling cap. If a patient has a scalp metastasis, they have Stage IV breast cancer.

Clinical Trials

I will discuss clinical trials. I have worked on clinical trials for breast cancer chemotherapy regimens. Generally speaking, there are three phases to clinical trials and drug development. Phase I involves testing a new drug to determine dosing of the drug. Phase II considers how well the drug works for therapy given cancer type and setting. Phase III addresses whether the drug or combination of drugs is better than the previous standard treatment. In most cases, the role of a phase III clinical trial for early breast cancer adjuvant chemotherapy drugs is to compare two treatment regimens to determine if one regimen has greater efficacy but not does not have an unacceptable increase in the side effect profile. The types of side effects that are most important to researchers are life-threatening side effects. As such, for a researcher on a clinical trial, alopecia rates are not a primary focus.

Each clinical trial will enroll a diverse and unique group of patients; we have learned with time that comparing the results of one trial with another introduces bias, is not valid, and can lead to erroneous conclusions. We have learned that sound conclusions regarding the relative efficacy and toxicity of two different regimens can only be obtained when the two groups are treated in the same trial and assignment of patients to each group is random.

Because alopecia is not a usual primary endpoint in clinical trials on breast cancer, comparing rates of ongoing alopecia after the completion of chemotherapy between one trial and another trial does not yield accurate conclusions. Reported rates of alopecia after the completion of chemotherapy may not be tracked consistently, or at all, particularly in patients in whom the disease progressed, who were on other regimens prior to the trial, or who continued on to other regimens or therapies after the trial.

When a clinical trial shows an efficacy benefit of one regimen over another in early breast cancer, with an acceptable side effect profile, that regimen is adopted by oncologists. Oncologists do not wait additional years before using that regimen to see what other potential side effects might emerge. This is because the goal of chemotherapy is to save lives. Lives would be lost through unnecessary delay in the adoption and use of effective regimens.

Taxotere Clinical Trials

TAX311

TAX 311 compared the observed overall response rate and toxicity profile of docetaxel to paclitaxel in patients with progressive breast cancer after one prior chemotherapy regimen given for metastatic or locally advanced disease, or who developed metastatic or locally advanced disease during or after completing an adjuvant chemotherapy regimen. Prior therapy must have included an anthracycline, unless medically contraindicated. The secondary objectives were to compare time to disease progression, duration of response, quality of life, and survival between the two treatment arms. From October 21, 1994 through October 3, 2001, 449 patients were randomized to receive either Taxotere (Arm A – 225 patients) or paclitaxel (Arm B – 224 patients). Taxotere was administered at a dose of 100 mg/m² as a one hour intravenous infusion. Paclitaxel was administered at a dose of 175 mg/m² given as a three hour infusion. Each regimen was given once every twenty-one days. Patients continued therapy until there was evidence of progressive disease, unacceptable toxicity, or the patient requested to be taken off the study.

Randomized patients on the Taxotere arm achieved an overall response rate of 32% vs. 25% on the paclitaxel arm. In the evaluable groups, defined as patients who met the major eligibility criteria, received a minimum of two cycles of therapy, had lesions assessed at least once after treatment began, and had no major protocol violations, these rates were 37% vs. 26%. The 11% difference in favor of Taxotere in the evaluable group achieved statistical significance ($p = 0.02$). Time to progression was significantly longer for the Taxotere group (median 172 days for Taxotere; 109 days for paclitaxel). This difference was likewise significant ($p < 0.01$ for intent-to-treat; $p < 0.001$ evaluable).

Tax 311 included data on alopecia generally. In May 1996, an interim analysis was performed that included the first 104 patients. At that point, the most commonly observed non-hematologic toxicities possibly or probably related to Taxotere/paclitaxel included alopecia (63.5% / 62.7%).

Sparano Papers

Several of Plaintiffs' experts rely on a 2008 publication from Sparano, et al.,³³ to support their contention that Taxol (paclitaxel) is superior to Taxotere (docetaxel). However, the Sparano paper provides no support for the position that Taxol is superior to Taxotere for the adjuvant treatment of breast cancer.

The rationale for conducting the Sparano study was that there were concerns that Taxol administered every three weeks (the FDA-approved dosing schedule) was not as effective

³³ Sparano, J., et al. Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer. *N Engl J Med.* 2008;358(16):1663-1671.

as Taxotere administered every three weeks or as effective as Taxol administered every week. In order to further analyze these concerns, Sparano and his colleagues designed a study to compare Taxol administered every three weeks with Taxol administered every week, docetaxel administered every three weeks, and docetaxel administered every week.

The study found that there was significantly better disease-free survival for both Taxol administered every week and Taxotere administered every three weeks as compared to Taxol administered every three weeks. The study did not compare Taxol administered every week with Taxotere administered every three weeks, so there is no basis to claim that Taxol administered every week would provide a survival benefit as compared to Taxotere administered every three weeks.

The Sparano paper was updated in 2015 with 12-year data.³⁴ The 12-year data confirmed the survival benefit seen in the earlier analysis for both Taxol administered every week and Taxotere administered every three weeks as compared to Taxol administered every three weeks. Again, Sparano's updated analysis did not compare Taxol administered every week with Taxotere administered every three weeks, so there is no basis to claim that Taxol administered every week would provide a survival benefit as compared to Taxotere administered every three weeks.

Taken collectively, the Sparano publications actually support that for the adjuvant treatment of breast cancer, Taxotere administered every three weeks provides a survival benefit compared to Taxol administered every three weeks.

TAX 316 (BCIRG 001)

TAX 316 was a clinical trial, performed by the Breast Cancer International Research Group, Ltd. and sponsored by Sanofi as part of its post-marketing commitment to the FDA, which looked at the efficacy of Taxotere in the adjuvant setting. This clinical trial was a multicenter Phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) as adjuvant treatment of operable breast cancer patients with positive axillary lymph nodes. Both regimens were administered for a total of six cycles unless treatment was precluded by relapse, subject refusal, or unacceptable toxicities. The primary objective was to compare disease-free survival (DFS). Overall survival (OS) was the main secondary objective and was defined as the time interval between the date of randomization and the date of death.

Enrollment for the TAX 316 study began in 1997 and concluded in 1999. A total of 1,480 patients (744 TAC / 736 FAC) were enrolled in the TAX 316 study. At the 55 month interim follow-up, disease-free survival was 75% among TAC-treated patients compared

³⁴ Sparano, J., et al. Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. J Clin Oncol. 2015;33(21):2353-2360.

to 68% among FAC-treated patients. This represented a 28% reduction in the risk of relapse. The efficacy benefits reported in the 55 month interim report were maintained in the 10-year follow up.³⁵

It is my understanding that Plaintiffs claim that the results of the TAX 316 study provide support for the position that docetaxel causes permanent alopecia. For a number of reasons, that is incorrect.

First, at the 55 month interim analysis, 3.0% (22/744) patients treated in the TAC regimen were recorded as having persistent alopecia and 3.9% (29/744) were recorded as having alopecia into the follow up period at the 10 year mark. This does not mean that 3.9% of patients remained without hair regrowth at 10 years. Instead, it means that when measured at any point into the follow up period, which could be as early as three months after chemotherapy treatment, a patient was recorded with alopecia and was never identified as having had that alopecia resolve. Without an affirmative report of resolution, their alopecia continued to be recorded as part of the 3.9% number. But because patients are lost to follow up, progressed to other chemotherapy treatments, or died, the 3.9% number cannot be interpreted as meaning that 3.9% of women had ongoing alopecia at 10 years. Consequently, the TAX316 study only reported on “ongoing” alopecia, it did not report on “permanent” or “persistent” alopecia. The distinction is important, because for the majority of patients identified as having “ongoing” alopecia, there is no documentary evidence to support any claim that those patients had alopecia more than six months after chemotherapy. **(Figure A).**

Second, all patients who were recorded as having persistent alopecia were also treated with doxorubicin and cyclophosphamide, both of which carry reports of persistent alopecia in patients not treated Taxotere.³⁶ As such, any alopecia that was attributable to the chemotherapy regimen would also be attributable to doxorubicin or cyclophosphamide.

Third, the difference in rates of reported alopecia after the completion of chemotherapy between the two arms is not statistically significant. In the FAC arm, which did not include treatment with Taxotere, the 55-month interim follow-up reported that 1.2% (9/736) of FAC patients experienced persistent alopecia, and 2.2% (16/736) of FAC patients experienced persistent alopecia at the 10-year mark.

³⁵ Mackey, J., et al. Adjuvant Docetaxel, Doxorubicin, and Cyclophosphamide in Node-Positive Breast Cancer: 10-year Follow-up of the Phase 3 Randomised BCIRG 001 Trial. *Lancet Oncol.* 2013;14(1):72-80.

³⁶ Masidonski, P., et al. Permanent Alopecia in Women Being Treated for Breast Cancer, *Clin J Oncol Nurs.* 2009;13(1):13-14; Yagata, H. Abstract P5-15-17: National survey long-term recovery from chemotherapy-induced hair loss in patients with breast cancer. *Cancer Research.* http://cancerres.aacrjournals.org/content/75/7_Supplement/P5-15-17; Kim, GM, et al. Chemotherapy-induced Irreversible Alopecia in Early Breast Cancer Patients. *Breast Cancer Res Treat.* 2017 Jun;163(3):527-533.

GEICAM 9805

GEICAM 9805, a compliment to the TAX 316 study, was the first taxane-based study to exclusively enroll women with node-negative early stage breast cancer that was considered to be at high risk for recurrence. The study was conducted by Grupo Espanol de Investigacion en Cancer de Mama, a Spanish non-profit scientific cooperative group devoted to breast cancer. The study was sponsored by Sanofi. The study compared disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to disease-free survival after treatment with 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) as adjuvant treatment of high risk operable breast cancer patients with negative axillary lymph nodes.

Enrollment for GEICAM 9805 began in 2001 and ended in 2003. A total of 1,060 patients (539 TAC / 521 FAC) were enrolled in the study. The study concluded that, as compared with adjuvant FAC, adjuvant TAC improved the rate of disease-free survival among women with high-risk, node-negative breast cancer. With respect to alopecia, like TAX 316, GEICAM 9805 recorded instances of persistent alopecia in both arms of the study. At the end of the 10 year follow-up period, 3 cases of persistent alopecia were observed in the TAC group (539) and 1 case of persistent alopecia in the FAC group (521).³⁷

Additionally, it is important to remember that patients in the TAC arm of this study received (“A”) doxorubicin and (“C”) cyclophosphamide in addition to (“T”) docetaxel. Both A and C carry reports of persistent alopecia. As such, any alopecia attributable to the chemotherapy regimen could be attributable to A or C. Finally, there is no statistical difference between the rates of alopecia between the two study arms.

FDA Regulation and Drug Development

Because of my work on clinical trials, I am familiar with aspects of FDA regulation. I will discuss drug development and FDA regulation.

The FDA approval process begins with an Investigational New Drug (IND) application. I will discuss this process, including the information the IND provides to the FDA.

Another part of the FDA approval process is the New Drug Application (NDA). The FDA must approve the NDA before the drug can be sold in the United States. I will discuss the NDA process, including the information that the NDA provides to the FDA. I will discuss continuing reporting requirements following approval of the NDA.

³⁷ Although the study notes that 9.2% of patients had persistent alopecia, it was measuring the number of ongoing cases of alopecia (49) from the group of patients in the safety population. The safety population (532) differs from the randomized TAC population (539) because some patients in the randomized population never received Taxotere treatment.

The underlying data from TAX 311, TAX 316, and GEICAM 9805 were all submitted to the FDA. Submitting underlying data from clinical trials to the FDA is common and accepted. When the FDA has access to the underlying data from a study, it cannot be said that this information was “suppressed,” and the FDA has the necessary information to make conclusions about the drug and labeling. Because this information was submitted to the FDA for Taxotere, the FDA had and has the information it needed in making labeling decisions.

Labels of Chemotherapy Drugs and Taxotere Label

I will discuss labels/prescribing information for chemotherapy drugs, including Taxotere. I will also discuss that the FDA works with companies, like Sanofi, in developing the label. As a practicing medical oncologist, I am familiar with the prescribing information (PI) for many chemotherapeutic drugs. Many chemotherapy drugs’ prescribing information warn of very severe life-threatening risks, such as toxic and septic death, heart failure, fatal gastrointestinal bleeding, pulmonary embolism, neurotoxicity. As a clinician, I warn my patients of these severe risks. Yet, despite these very severe risks, nearly all of my patients choose to have chemotherapy. This is because killing cancer cells is the primary focus of cancer treatment.

In addition to warning of very severe side effects, many chemotherapy drugs’ prescribing information contain warnings about alopecia. For example, the prescribing information for doxorubin states, “Your hair may re-grow after your treatment.” Likewise, the label for cyclophosphamide states that alopecia “occurs commonly.” And the label for Taxol states that alopecia has been “observed in almost all patients.”

Similarly, information regarding alopecia has always been included on the Taxotere label. “Alopecia” was listed as an adverse reaction in the PI beginning in 2003. The label also stated, “Once you have completed all of your treatments, hair generally grows back.” I interpret “hair generally grows back” as leaving open the possibility that hair may not grow back.

In 2004, when Taxotere was approved for the adjuvant treatment of breast cancer, Sanofi submitted a proposed label that included the addition of adjuvant side effects data and persistent alopecia information from TAX 316. The FDA approved some portions of the proposed label. Yet, the FDA removed the proposed section of the label relating to “other persistent reactions,” which discussed persistent alopecia. Nevertheless, cases of “persistent alopecia” have been reported on the label since 2004.

Then, in May 2010 “hair loss” was listed in the patient counseling information and the FDA struck the language which included the phrase “hair generally grows back.” In 2015 the label was revised to include a statement that “cases of permanent alopecia have been reported.”

Case reports of adverse events are on the low end of the evidentiary hierarchy and do not establish causation. Moreover, the 2015 label modification is not supplemental or inconsistent with the information provided in prior iterations of the label.

The Taxotere label has always been consistent with the known side effect risk profile for Taxotere.

As a practicing medical oncologist, I have always understood the language in the PI to mean there can be circumstances that the hair may not grow back. “Alopecia” is a medical term, which simply means hair loss. There is no temporal element associated with the medical term alopecia.

The modifications that have occurred to the Taxotere label regarding alopecia have had no impact on my practice or my decision to use Taxotere. The changes that have occurred to the Taxotere label regarding alopecia have had no impact on the discussions I have with my patients regarding the side effects of Taxotere. The benefit/risk profile of Taxotere remains the same. Taxotere containing regimens to treat both HER2+ and HER2- breast cancer in an adjuvant setting are among the optimal regimens.

Dosing

For Taxotere-containing regimens, the dose should be 75 mg/m². A dose of 100 mg/m² is not on label.

Sources of Information Available to Medical Oncologists

Very frequently, side effects from chemotherapy drugs emerge after clinical trials and FDA approval. These types of side effects are called post-marketing side-effects. Oncologists typically learn about these side effect from sources other than the drug manufacturer. This is because many sources of information are available to oncologists, including their own clinical experience, medical literature, discussions with colleagues, and oncology meetings. Oncologists often learn about post-marketing side effects through those sources, not from label changes or the drug manufacturer. An example of a post-marketing side effect was the cardiac toxicity seen from Adriamycin.

Sales Representatives and Marketing

Oncologists do not base treatment-related decisions on marketing materials from pharmaceutical companies or contact with sales representatives. Instead, oncologists make treatment-related decisions based on their training, experience, clinical trials, and reliable medical literature.

II. CASE-SPECIFIC OPINIONS

Tanya Francis

I will offer case-specific opinions regarding Ms. Francis that are based on my review of her medical records, discovery responses, and depositions, my education, training, clinical experience, review of medical and scientific literature, and information presented at various medical forums. I will offer opinions regarding her breast cancer, treatment, and alopecia.

Ms. Tanya Francis is a 46-year-old African American female with a history of smoking, obesity, high blood pressure, diabetes, and high cholesterol. She underwent a total hysterectomy with bilateral salpingo oophorectomy in 2012, which created a post-menopausal state.

Ms. Francis's history of morbid obesity, hypertension, lipid abnormalities, and pre-diabetes led her to be diagnosed with metabolic syndrome in 2009. Metabolic syndrome consists of a cluster of conditions including high blood pressure, elevated glucose levels, excess body fat around the waist, and abnormal cholesterol or triglyceride levels.

Tanya Francis was 38 years-old when she was diagnosed in 2009 with stage IIB, estrogen and progesterone positive, and HER2 negative carcinoma in her left breast.³⁸ Her cancer was lobular carcinoma. The tumor measured 2 cm. She had one positive lymph node.

Before undergoing chemotherapy, Ms. Francis had surgery. Ms. Francis was given the option between a lumpectomy and mastectomy, which would have provided equivalent survival chances. She opted for a mastectomy.³⁹

A. Tanya Francis Required Chemotherapy with Taxotere to Optimize Her Survival

Ms. Francis needed chemotherapy to optimize her survival. Her treating oncologist Dr. Verghese also believed that Ms. Francis needed chemotherapy.⁴⁰ During her treatment, Ms. Francis developed deep vein thrombosis ("DVT"). Consequently, because of potential complications, Dr. Verghese raised her case with the hospital Tumor Board.⁴¹ The Tumor Board consisted of approximately ten trained oncologists.⁴²

The Tumor Board discussed Ms. Francis's case, and agreed with Dr. Verghese's recommendation that she receive six cycles of the combination regimen "TAC" every 21

³⁸ University Medical Center New Orleans, at 379-38.

³⁹ University Medical Center New Orleans, at 434-437.

⁴⁰ University Medical Center New Orleans, at 477-479.

⁴¹ University Medical Center New Orleans, at 477-479.

⁴² Cherian Verghese Dep. at 158:13-25, 159:1-22.

days.⁴³ The “TAC” regimen includes three separate medicines administered by IV: docetaxel (Taxotere), doxorubicin (Adriamycin), and cyclophosphamide.⁴⁴

I agree with the Tumor Board that Ms. Francis was best served with a taxane-containing regimen. If she had received a regimen without taxanes, such as AC or CMF, she would have had a reduced chance of survival.

B. Taxotere Was A Better Choice for Tanya Francis Than Paclitaxel, Which Would Have Increased Her Risk of Neuropathy

Ms. Francis has health issues that make Taxotere-containing regimens a better choice for her over Taxol-containing regimens. Notably, Ms. Francis was pre-diabetic when diagnosed with cancer. Because Taxol has a greater rate of neuropathy than Taxotere, Ms. Francis would have had a higher risk of neuropathy if she were given Taxol.

In addition, pre-diabetic patients are at an increased risk of becoming diabetic during steroid therapy. Because Taxol is administered on a weekly basis, steroid exposure is greater. For a Taxotere containing regimen, steroid exposure is 3 days out of every 3 weeks, for a Taxol containing regimen, steroid exposure is 3 days out of every week.

Following chemotherapy, Ms. Francis developed neuropathy and was prescribed Neurontin for her neuropathic pain.⁴⁵ Thus, it is apparent that it was appropriate to consider the risk of neuropathy when choosing Ms. Francis’s chemotherapy regimen. Ms. Francis also developed lymphedema, and was referred to spine massage and lymphedema compression treatment in November 2011 for increasing lymphedema.⁴⁶

I believe that Ms. Francis was an appropriate candidate for chemotherapy with Taxotere. A taxane containing regimen was optimal, and Taxotere reduced risks associated with both neuropathy and steroid exposure.

C. Dr. Verghese and Ms. Francis Decided to Move Forward with Chemotherapy Following an Informed Consent Process

Ms. Francis gave her informed consent to Dr. Verghese to proceed with chemotherapy notwithstanding its risks. Before receiving chemotherapy, Ms. Francis was warned of the risk of alopecia. Dr. Verghese testified that he read the package insert (or labeling) for Taxotere “at some time or the other, yes.”⁴⁷ However, Dr. Verghese does not remember reading the Taxotere label in its entirety, because “the labeling goes from studies, dosing protocols, diluents and IV fluids, which don’t really translate to any relevant changes in

⁴³ Cherian Verghese Dep. at 158:13-25, 159:1-22.

⁴⁴ University Medical Center New Orleans, at 518.

⁴⁵ University Medical Center New Orleans, at 315-316; University Medical Center New Orleans, at 297-300.

⁴⁶ University Medical Center New Orleans, at 411-412.

⁴⁷ Cherian Verghese Dep. 41:21-24.

treatment.”⁴⁸

In 2009, the labels for the chemotherapy drugs Ms. Francis took warned of alopecia. In 2009, the FDA-approved label for Adriamycin included that “Patients should be informed that they will almost certainly develop alopecia.” In 2009, the FDA-approved label for cyclophosphamide included “Adverse Reactions,” reading, “Alopecia occurs commonly in patients treated with cyclophosphamide. The hair can be expected to grow back after treatment with the drug or even during continued drug treatment, though it may be different in texture or color.”

In 2009, the FDA-approved label for Taxotere included “Adverse Reactions,” reading that the “[m]ost common adverse reactions are...alopecia.”⁴⁹ Information on alopecia was included in various other parts of the label.⁵⁰ In the Patient Counseling Information section it stated: “Loss of hair occurs in most patients taking Taxotere (including hair on your head, underarm, pubic hair, eyebrows, and eyelashes). Hair loss will begin after the first few treatments and varies from patient to patient. Once you have completed all your treatments, hair generally grows back.”⁵¹

Dr. Verghese did not rely on the company or its sales representatives to provide updates on changes to the labeling of a drug.⁵² As is the standard in oncology practice, Dr. Verghese reviewed journal updates, case reports, and peer reviewed and non-peer reviewed publications, to learn about post-marketing side effects.⁵³ Dr. Verghese testified that major publications “bring out the major side effects,” which include “organ failure . . . hepatitis, or anything that can compromise a patient’s life.”⁵⁴

Dr. Verghese discussed his practice in warning patients of side effects. Dr. Verghese testified that he has a “comprehensive discussion” with patients regarding side effects, but does not verbally warn breast cancer patients of every potential side effect they may experience.⁵⁵

Dr. Verghese discusses the “major things, because a lot of people want to know what the common side effects are,” and then provides a “copy of all the side effects” for the patient to review at her home.⁵⁶ No matter the discussion, Dr. Verghese tells patients that there may also be “new side effects that we don’t know of.”⁵⁷

⁴⁸ Cherian Verghese Dep. 139:7-10.

⁴⁹ Taxotere Label (09/2007).

⁵⁰ Taxotere Label (09/2007).

⁵¹ Taxotere Label (09/2007).

⁵² Cherian Verghese Dep. 45:16 – 46:10.

⁵³ Cherian Verghese Dep. 46:20 – 47:23.

⁵⁴ Cherian Verghese Dep. at 47:15 – 48:6.

⁵⁵ Cherian Verghese Dep. 143:15 – 144: 12.

⁵⁶ Cherian Verghese Dep. at 143:21-25.

⁵⁷ Cherian Verghese Dep. at 144:6-12.

Dr. Verghese was aware of the possibility of alopecia and warned Ms. Francis regarding alopecia. At the time Dr. Verghese prescribed Taxotere for Ms. Francis, it was his general understanding that alopecia was a common side effect – but he “would not call it temporary. I never tell people that it’s temporary.”⁵⁸

Instead, Dr. Verghese tells patients that hair loss “depends on multiple factors, your other medical problems, your deficiencies. You may be vitamin deficient. We don’t know anything about these things. So multiple factors go into how you react, how deep the reaction is, and how long it takes for things to turn around. Even though all these people say it’s temporary and all that, there’s multiple factors involved, so I don’t use the word temporary. I even tell them, you know, hair may come back, and it may look totally different.”⁵⁹

Dr. Verghese sets the expectations of his patients clearly, explaining: “I tell them that expecting not to lose hair, expecting the hair to look the same, these are all unreal expectations. We have to treat this, and you will have hair-related problems. If they tell me - - if they ask me whether their hair loss is going to be permanent, then I tell them, even though there aren’t - - I’m not going to take a chance on that, and that’s where the wig comes in. So the discussion is a little different from saying it may be permanent or never permanent. I tell them it’s better to take a different approach to some of these side effects.”⁶⁰

Before her first chemotherapy treatment, Ms. Francis again reviewed the side effects of chemotherapy with Nurse Celeste Keller.⁶¹ This discussion included the management of nausea and vomiting, unusual fever, bleeding, bruising, neutropenia, infusion related reactions, and thrombocytopenia. In addition, Ms. Keller advised Ms. Francis that “total hair loss” would occur in 2-3 weeks, and suggested she purchase wigs and scarfs or hats.⁶²

If Ms. Francis had requested a Taxol-containing regimen and raised a concern with Taxotere and hair loss, Dr. Verghese would have counseled her that “both of them cause hair loss. Even though one may be more than the other, both cause hair loss. So if I were to see hair loss in one, I would predict hair loss in the other one too, so my recommendation is just to make a wig all the time.”⁶³

I agree with this appraisal, specifically, that there is no promise of better hair regrowth with paclitaxel over Taxotere. It is not my practice, nor have I seen evidence, that permanent alopecia is more common following docetaxel than paclitaxel, cyclophosphamide, or doxorubicin.

⁵⁸ Cherian Verghese Dep. 102:17 – 103:5.

⁵⁹ Cherian Verghese Dep. 103:7-18.

⁶⁰ Cherian Verghese Dep. 104:23 – 105:16.

⁶¹ University Medical Center New Orleans, at 518.

⁶² University Medical Center New Orleans, at 518.

⁶³ Cherian Verghese Dep. 109:2-12.

Ms. Francis accepted many significant potential side effects by undergoing chemotherapy. Notably, she accepted the possibility of death.

While all chemotherapy has risks and potential complications, Ms. Francis was appropriately informed of these risks prior to choosing to undergo chemotherapy with Taxotere. The benefits outweighed the risks for her and she was appropriately counseled on the potential risks and complications of the treatment.

D. Tanya Francis's Course of Care After Chemotherapy Demonstrates No Persistent Alopecia Attributable to Chemotherapy Alone

Ms. Francis claims she experienced total hair loss after receiving her first TAC infusion.⁶⁴ Her alopecia continued during chemotherapy treatment.⁶⁵ Three months after Ms. Francis completed chemotherapy, a radiation oncology nurse noted ongoing alopecia on Ms. Francis's head and body.⁶⁶

In July 2013, Ms. Francis visited her medical oncologist for a follow-up appointment, and "when asked if she has any other pain, . . . stated 'yes, my head. I busted a sore on my head and fluid came out.'"⁶⁷ This record does not note ongoing alopecia, or a concern with hair loss in conjunction with these scalp sores.

Dr. Collins Burrow, Ms. Francis's second oncologist, noted "patient reports using hair dye and chemical perm on regular basis."⁶⁸ Dr. Collins Burrow does not remember "Ms. Francis coming in without something on her head that resembled, I mean, hair. I don't recall her as - - my recollection is that she - - if she, in fact, has alopecia, she wears a prosthesis."⁶⁹

In June 2017, Ms. Francis visited her primary care physician for "marks on hands and scalp" and requested a referral to a dermatologist.⁷⁰ Dr. Tillery referred Ms. Francis to Dimitri Dermatology.⁷¹ During this initial consultation and subsequent treatment, Ms. Francis did not mention chemotherapy as a possible cause of her hair loss.⁷²

⁶⁴ University Medical Center New Orleans, at 343-344.

⁶⁵ University Medical Center New Orleans, at 343-344; University Medical Center New Orleans, at 346-347; University Medical Center New Orleans, at 349-350; University Medical Center New Orleans, at 355-356; University Medical Center New Orleans, at 370-371; University Medical Center New Orleans, at 373-374; University Medical Center New Orleans, at 376-377.

⁶⁶ Tulane Cancer Center Clinic, at 304-305.

⁶⁷ Tulane Cancer Center Clinic, at 99-103.

⁶⁸ Tulane Cancer Center Clinic, at 99-103.

⁶⁹ Collins Burrow Dep. 81:19-25.

⁷⁰ Bertrand Tillery Dep. 53-56.

⁷¹ Bertrand Tillery Dep. 53-56.

⁷² Janice Birkhoff Dep. 88:3-8.

In sum, the chronology, including photographs of Ms. Francis before and following treatment, demonstrate that her hair grew back after chemotherapy, and that any subsequent changes in her hair are not associated with this fixed period in time of her treatment.

E. Tanya Francis's Course of Care After Chemotherapy Included Hormone Therapy

Given Ms. Francis's estrogen and progesterone positive status, Ms. Francis required hormonal therapy for her cancer, and was prescribed Tamoxifen.

Before prescribing Tamoxifen to Ms. Francis, Dr. Verghese discussed the risks and benefits of the medication – including the possibility Tamoxifen might cause additional blood clots, uterine cancers, and hair thinning.⁷³

On November 18, 2009, Ms. Francis started Tamoxifen 20 mg, once a day.⁷⁴ In October 2010, Ms. Francis was observed to have enlarged ovaries.⁷⁵ This observation, in combination with her history of estrogen and progesterone positive cancer, led Ms. Francis to have a hysterectomy and bilateral salpingo-oophorectomy on June 18, 2012.⁷⁶ After this surgery, Ms. Francis was able to change her hormonal treatment to an aromatase inhibitor.

In July 2012, Ms. Francis saw her oncologist, Dr. Collins-Burrow, for a follow-up appointment related to her breast cancer.⁷⁷ At this visit, Ms. Francis and Dr. Collins-Burrow discussed her recent hysterectomy, and determined she would stop taking Tamoxifen, as she had been surgically rendered post-menopausal, and begin 1 mg Arimidex daily.⁷⁸

In July 2012, the Arimidex labeling listed “hair thinning (alopecia)” as an adverse event.⁷⁹

After five years, Ms. Francis discussed the risks and benefits of continuing hormone therapy with her oncologist and opted to continue hormone therapy to lower her risk of recurrence.⁸⁰

F. Summary of Opinions

There is no medically reliable way to attribute Ms. Francis's hair loss complaint to Taxotere alone. Ms. Francis needed chemotherapy for optimal survival. She required a taxane-

⁷³ Cherian Verghese Dep. 160:19 – 162:24.

⁷⁴ University Medical Center New Orleans, at 481-482; Tulane Cancer Center Clinic, at 127-131.

⁷⁵ University Medical Center New Orleans, at 611-614.

⁷⁶ University Medical Center New Orleans, at 244-246; 698-699.

⁷⁷ Tulane Cancer Center Clinic, at 127-131.

⁷⁸ Tulane Cancer Center Clinic, at 127-131.

⁷⁹ Arimidex Labeling (04/2011).

⁸⁰ Tulane Breast and Surgery Clinic, at 5-9.

containing regimen to prevent recurrence. A Taxotere-containing regimen was among the best choices for her treatment, and had the advantage of reduced risk of neuropathy and less exposure to steroids.

While all chemotherapy has risks and potential complications, Ms. Francis was appropriately informed of these risks prior to choosing to undergo chemotherapy with Taxotere. The available label at the time of treatment adequately apprised medical oncologists of the risk of alopecia. The goal of Ms. Francis's therapy was to prevent relapse of her cancer, and to date, her cancer has not relapsed and the goal appears to have been achieved.

Antoinette Durden

I will offer case-specific opinions regarding Ms. Antoinette Durden that are based on my review of her medical records, discovery responses, depositions, my education, training, clinical experience, review of medical and scientific literature, and information presented at various medical forums. I will offer opinions regarding her breast cancer, its treatment, and her alopecia.

Ms. Durden is an African American female who is 68 years old, post-menopausal, with a medical history of obesity, high blood pressure, heart murmur, osteoarthritis, vitamin D deficiency, and various dermatological fungal infections and rashes.

In 2011, Ms. Durden was diagnosed with breast cancer. She had infiltrating ductal carcinoma in her left breast that measured 2.5 cm.⁸¹ Ms. Durden's breast cancer was ER+, PR+, and HER2-. She had one lymph node that tested positive for cancer.

Ms. Durden needed surgery, chemotherapy, and hormonal directed therapy for her early breast cancer.

A. Ms. Durden Chose the Most Aggressive Surgical Option Offered to Her, Despite the Cosmetic Effects

Ms. Durden's surgeon, Dr. Riker, informed Ms. Durden that she had several surgical options, including a lumpectomy with radiation (that would have conserved her breast), mastectomy, or bilateral mastectomy.⁸²

Ms. Durden had an extensive family history of serious and fatal cancer, including breast cancer. At the time of Ms. Durden's diagnosis, two nieces and a sister had been diagnosed with breast cancer.⁸³ An aunt died of lung cancer, and her brother had recently been

⁸¹ Ochsner Health System, at 2541-2542.

⁸² Infusion Pharmacy, Ochsner Baptist Medical Center, at 303-305; Prier Dep. 36:7-37:20.

⁸³ Ochsner Health System, at 2570-2575; Durden Dep. 88:21-89:2; 107:25-108:3.

diagnosed with bone cancer.⁸⁴

Considering her family history and increased risk of breast cancer, and seeking to eliminate the possibility that cancer would develop in her right breast, Ms. Durden elected to have a prophylactic right mastectomy in addition to a left mastectomy.⁸⁵ Ms. Durden indicated she did not want to live with the fear that her cancer might recur.⁸⁶

Dr. Riker performed these surgeries, along with bilateral sentinel node biopsies, on July 20, 2011.⁸⁷ Following the surgeries, the lymph node pathologies showed that Ms. Durden had an involved lymph node and stage IIB, ER+, HER2-negative infiltrating moderately differentiated ductal adenocarcinoma of the left breast.⁸⁸

Prior to surgery, Dr. Riker also discussed the possibility of chemotherapy with Ms. Durden, noting that it might reduce the chance of a cancer recurrence.⁸⁹ He referred Ms. Durden to Dr. Sophy Jancich to discuss adjuvant chemotherapy options.⁹⁰

B. Taxotere with Cytosan Was an Optimal Option to Treat Ms. Durden's Cancer

1. Ms. Durden Was Offered, and Refused, a Chemotherapy Regimen Including Taxol and Adriamycin

During Ms. Durden's initial meeting with Dr. Jancich to discuss chemotherapy regimens, Dr. Jancich suggested Ms. Durden enroll in the clinical trial S0221 - a phase II clinical trial comparing four dosing schedules of doxorubicin and cyclophosphamide (AC) followed by paclitaxel.⁹¹ Ms. Durden discussed S0221 with Dr. Jancich over several appointments.⁹²

Ms. Durden's daughter, Anesha Prier, worked as a cancer navigator for the Louisiana Breast and Cervical Health Program ("LBCHP"), then part of Louisiana State University hospital.⁹³ Ms. Prier was familiar with doxorubicin (Adriamycin) through her work as a cancer navigator.⁹⁴ Dr. Jancich, Ms. Durden, and her daughter were all aware that Adriamycin was also referred to as the "Red Devil" due to its side effects.⁹⁵ Those side

⁸⁴ Ochsner Health System, at 2571; Durden Dep. 108:11-108:16.

⁸⁵ Prier Dep. 37:21-39:15; Infusion Pharmacy, Ochsner Baptist Medical Center, at 303-305.

⁸⁶ Durden Dep. 239:15-240:14.

⁸⁷ Ochsner Health System, at 2557-2559.

⁸⁸ Infusion Pharmacy, Ochsner Baptist Medical Center, at 405-411, 422-426.

⁸⁹ Prier Dep. 37:4-37:16.

⁹⁰ Infusion Pharmacy, Ochsner Baptist Medical Center, at 263-264.

⁹¹ Ochsner Health System, at 2577; Infusion Pharmacy, Ochsner Baptist Medical Center, at 257-261; PPR, at 452; Ochsner Health System, at 2607-2609; Jancich Dep. at Ex. 5 33:58-64.

⁹² Ochsner Health System, at 2577; Infusion Pharmacy, Ochsner Baptist Medical Center, at 257-261; PPR, at 452; Ochsner Health System, at 2607-2609; Jancich Dep. at Ex. 5 33:58-64.

⁹³ Prier Dep. 14:5-14:11; Prier Dep. 19:3-15.

⁹⁴ Prier Dep. 50:9-53:2.

⁹⁵ Jancich Dep. 161:21-164:4; Durden Dep. 252:25-254:12; Prier Dep. 50:9-53:2.

effects include a risk of significant heart damage, as well as risks of severe nausea, vomiting, and fatigue.⁹⁶ Adriamycin also increases the risk of acute leukemia associated with chemotherapy. Ms. Prier had personally witnessed the drug's harsh side effects on cancer patients.⁹⁷ She did not want her mother, Ms. Durden, to experience these side effects.⁹⁸

Ms. Durden's family history of heart disease was also a concern.⁹⁹ In particular, Ms. Durden's sister was diagnosed with breast cancer and received treatment, only to later die of a myocardial infarction.¹⁰⁰ Ms. Durden also had cardiac concerns of her own – including years of treatment for hypertension.¹⁰¹

Given Ms. Durden's extensive family and personal history of heart disease, Adriamycin's potentially fatal cardiotoxicity was of particular concern.¹⁰² As Ms. Prier explained, she was "concerned about [Ms. Durden] taking Adriamycin due to the family history of hypertension," and "her own hypertension as well [...] You don't want to put extra stress on a heart that already isn't beating or working as well as it should be."¹⁰³

Due to these concerns, Ms. Durden and her daughter were "adamant that they do not want to receive Adriamycin containing regimen."¹⁰⁴ Given Ms. Durden's personal history of heart disease, she made a reasonable choice by avoiding Adriamycin. She has mild concentric left ventricular hypertrophy and a systolic ejection murmur. She has a family history of heart disease. Her heart issues would have placed her at an even greater risk of cardiac toxicity if she took Adriamycin. By avoiding Adriamycin, Ms. Durden avoided the increased risk of cardiac toxicity and leukemia. The doctor's prescribing decision was appropriate in this context.

In addition, Ms. Durden is pre-diabetic. Because Taxol has higher rates of neuropathy than Taxotere and she was already at an increased risk of neuropathy, Ms. Durden's risk of developing neuropathy was lowered by taking Taxotere.

2. Taxotere with Cytosan Was the Best Regimen for Ms. Durden's Cancer Given Her Refusal of Adriamycin Therapy

Dr. Jancich relied on the NCCN Guidelines list of "preferred" regimens for the adjuvant

⁹⁶ Jancich Dep. 161:21-164:4; Prier Dep. 50:9-53:2.

⁹⁷ Prier Dep. 50:9-53:2.

⁹⁸ Prier Dep. 50:9-53:2.

⁹⁹ Prier Dep. 54:18-58:16; Durden Dep. 88:1-3; 88:18-20; Ochsner Health System, at 2543-2548.

¹⁰⁰ Ochsner Health System, at 2570-2571; Prier Dep. 56:556:21.

¹⁰¹ Walgreens, at 65; Ochsner Health System, at 2543-2548; Ochsner Health System, at 2590-2593; Ochsner Health System, at 2594; Prier Dep. 58:7-58:16.

¹⁰² Prier Dep. 54:18-58:23.

¹⁰³ Prier Dep. 58:17-23.

¹⁰⁴ Ochsner Health System, at 2607-2609; Ochsner Health System, at 2616-2618; Infusion Pharmacy, Ochsner Baptist Medical Center, at 257-260.

treatment of HER2-negative early breast cancer when determining the appropriate treatment regimen for Ms. Durden.¹⁰⁵ In 2011, the NCCN Guidelines listed five “preferred” regimens for adjuvant treatment of HER2-negative breast cancer.¹⁰⁶ The only “preferred” regimen that did not include Adriamycin was the “TC” regimen, consisting of Taxotere (docetaxel) and Cytosan (cyclophosphamide).¹⁰⁷ This is because there were no randomized trials demonstrating the effectiveness of Taxol in a regimen that did not contain anthracyclines. Therefore, based on Ms. Durden’s refusal of Adriamycin, the only available preferred and proven effective regimen was the “TC” regimen.

In September 2011, Dr. Jancich noted that Ms. Durden and her daughter were “adamant that they do not want to receive Adriamycin containing regimen.”¹⁰⁸ Dr. Jancich concluded simply: “Therefore, [Ms. Durden] will receive TC (docetaxel 75mg/m² /Cytosan 600mg/m²) every 21 days x6.”¹⁰⁹ Again, on October 7, 2011, Dr. Jancich noted: “[Ms. Durden]’s daughter and [Ms. Durden] have elected not to receive Adriamycin-containing regimen due to potential adverse side effects. After detailed discussion regarding potential adverse side effects, [Ms. Durden] is adamant about not receiving Adriamycin-containing regimen.”¹¹⁰

Dr. Jancich testified that AC followed by Taxol and “TC” (Taxotere and Cytosan) were the two options offered to Ms. Durden, and Ms. Durden refused AC.¹¹¹ Dr. Jancich’s prescription followed: “[Ms. Durden] will be scheduled to begin TC (docetaxel 75mg per meter square/Cytosan 600mg per meters square every 21 days for six cycles tentatively scheduled to begin 10/18/2011.”¹¹²

3. Dr. Jancich’s Decision Regarding Treatment was Appropriate and Reasonable

Ms. Durden testified that she would have still elected to receive chemotherapy.¹¹³ The only established chemotherapy regimen for early breast cancer that does not contain either Adriamycin or a taxane is CMF. This CMF regimen could have theoretically been used in Ms. Durden’s case, but is believed to be inferior to taxane based chemotherapy regimens, based on the available data, and is associated with a lower cure rate. This is why it was not listed as a preferred regimen by NCCN, and why TC was chosen for her treatment.

TC was an NCCN-preferred regimen in 2011, and remains an NCCN-preferred regimen

¹⁰⁵ Jancich Dep. 187:18-187:24.

¹⁰⁶ NCCN Guidelines, at § BINV-K (2011).

¹⁰⁷ NCCN Guidelines, at § BINV-K (2011); Jancich Dep. 192:10-192:21.

¹⁰⁸ Ochsner Health System, at 2607-2609.

¹⁰⁹ Ochsner Health System, at 2607-2609.

¹¹⁰ Ochsner Health System, at 2616-2618.

¹¹¹ Jancich Dep. 181:17-182:17; Jancich Dep. 168:1-168:3; Jancich Dep. 258:2-21.

¹¹² Ochsner Health System, at 2616-2618.

¹¹³ Durden Dep. 216:11-216:15.

for good reason.¹¹⁴ Current NCCN Guidelines list only three preferred regimens for adjuvant treatment of HER2-negative breast cancer, and TC remains the only option that does not include Adriamycin.¹¹⁵ The other two options each consist of dose-dense Adriamycin and Cytosan (“AC”) followed by Taxol.¹¹⁶ TC remains the only preferred regimen for a patient like Ms. Durden who refuses Adriamycin even today, more than seven years after Ms. Durden’s treatment.

TC has an overall survival benefit when compared with AC.¹¹⁷ AC, in turn, has proven possible survival benefit and some side effect advantages over older generation treatment regimens like CMF (cyclophosphamide, methotrexate, and 5-fluorouracil). Thus, it is accepted that TC is a preferable option to older generation, non-taxane regimens such as CMF, as reflected in its long-standing status as an NCCN “preferred” regimen and the fact that Dr. Jancich did not discuss or report considering CMF when prescribing chemotherapy for Ms. Durden.¹¹⁸

If Ms. Durden were given a chemotherapy regimen that did not contain a taxane, she would have reduced her odds of survival. Dr. Jancich’s decision to prescribe TC was appropriate.

C. Dr. Jancich and Ms. Durden Decided to Move Forward with Chemotherapy Following an Informed Consent Process

Ms. Durden gave her informed consent to proceed with the TC regimen. Dr. Jancich reviewed a Consent to Administration of Chemotherapy form with Ms. Durden, which identified docetaxel and cyclophosphamide as the drugs Ms. Durden consented to receive.¹¹⁹ The form listed “hair loss” as the first of “risks and discomforts” associated with chemotherapy treatment.¹²⁰ In addition to “hair loss,” the form listed many potentially severe and long-lasting side effects including “[d]amage to bone marrow (blood forming organ),” “[d]amage to body organ such as brain, heart kidneys, liver, lungs, nervous system, skin,” “[s]terility,” “[l]oss of lining of the intestinal tract from mouth to anus,” “[s]econdary cancer (a cancer in the future that may be caused by chemotherapy),” and “[d]eath.”¹²¹

The Taxotere label in effect when Ms. Durden was prescribed Taxotere warns of hair loss

¹¹⁴ NCCN Guidelines, at § BINV-K (2011); NCCN Guidelines, at § BINV-K (2018).

¹¹⁵ NCCN Guidelines, at § BINV-K (2018).

¹¹⁶ NCCN Guidelines, at § BINV-K (2018).

¹¹⁷ Jones et al., Docetaxel with Cyclophosphamide Is Associated with an Overall Survival Benefit Compared with Doxorubicin and Cyclophosphamide: 7 Year Follow-up of U.S. Oncology Research Trial 9735, 27 J. CLIN. ONCOL. 1177-83 (2009); Jones et al., Phase III Trial Comparing Doxorubicin Plus Cyclophosphamide with Docetaxel Plus Cyclophosphamide as Adjuvant Therapy for Operable Breast Cancer, 24(34) J. CLIN ONCOL. 5381-87 (2006).

¹¹⁸ Jancich Dep. 181:17-182:17; Jancich Dep. 258:2-21.

¹¹⁹ Ochsner Health System, at 2673-2674.

¹²⁰ Ochsner Health System, at 2673-2674.

¹²¹ Ochsner Health System, at 2673-2674.

alongside other potentially severe and long-lasting side effects such as fatal anaphylaxis, toxic or septic death, fatal gastrointestinal bleeding, hepatic impairment, acute myeloid leukemia, severe hypersensitivity, grade 4 neutropenia, severe drug-induced thrombocytopenia, and severe neurosensory symptoms, including severe motor neuropathy.¹²²

The Taxotere label in effect at the time of Ms. Durden's treatment stated that the "[m]ost common adverse reactions across all TAXOTERE indications are [...] alopecia."¹²³ The Patient Counseling Information portion of the label instructed physicians to "[e]xplain to patients that side effects such as [...] hair loss are associated with docetaxel administration."¹²⁴ The Patient Information portion of the label states that "The most common side effects of TAXOTERE include: [...] hair loss."¹²⁵ At the time of Ms. Durden's treatment, Dr. Jancich did not look at chemotherapy labels directly, and instead obtained label information from UpToDate.¹²⁶

Dr. Jancich counseled patients that "hair generally grows back" after chemotherapy treatment, and she testified that she would not have told patients that their hair would grow back one hundred percent.¹²⁷

Ms. Durden was given a booklet from the American Cancer Society describing chemotherapy and its side effects.¹²⁸ The booklet stated: "In most cases, hair grows back after chemo."¹²⁹ Ms. Durden was also provided with a handout from the website chemocare.com listing "hair loss" as a side effect of Taxotere.¹³⁰

Ms. Durden testified that at least a year prior to her chemotherapy, one of her nieces had been treated with Taxotere and had experienced permanent hair loss. Ms. Durden testified that this was not a factor in her decision to undergo chemotherapy.¹³¹

While all chemotherapy has risks and potential complications, Ms. Durden was appropriately informed of these risks prior to choosing to undergo chemotherapy with Taxotere. The benefits outweighed the risks for her and she was appropriately counseled on the potential risks and complications of the treatment. The available label at the time of treatment (and at the time Dr. Jancich may have read portions of it) adequately apprised medical oncologists of the risk of alopecia. As a medical oncologist, the label cannot and does not impact your prescribing practices of counseling if you do not read it or have not

¹²² Taxotere label (09/2011).

¹²³ Taxotere label (09/2011).

¹²⁴ Taxotere label (09/2011).

¹²⁵ Taxotere label (09/2011).

¹²⁶ Jancich Dep. 119:19-120:20; 126:6-127:10.

¹²⁷ Jancich Dep. at 129:17-130:12; Jancich Dep. 238:17-239:2.

¹²⁸ PPR, at 963.

¹²⁹ PPR 973.

¹³⁰ PPR 695.

¹³¹ Durden Dep. 81:8-81:20.

read it since it changed.

D. Ms. Durden's Persistent Alopecia Is Not Attributable to Chemotherapy

Ms. Durden testified that all of her hair fell out during chemotherapy, and she was completely bald.¹³² There is no note or mention of persisting hair loss secondary to chemotherapy in Dr. Jancich's records of her treatment of Ms. Durden from 2012 to 2015. With thorough work up and evaluation, none of Ms. Durden's treating dermatologists attributed her hair loss to chemotherapy. They in fact diagnosed Ms. Durden with alopecia from multiple other causes.

E. Ms. Durden's Course of Care After Chemotherapy Included Hormonal Treatment

Because Ms. Durden's cancer is estrogen and progesterone positive, she needed hormonal treatment. After chemotherapy, Dr. Jancich prescribed endocrine therapy with letrozole for Ms. Durden, beginning on February 23, 2012.¹³³ Ms. Durden took letrozole for more than 5 years, and completed letrozole therapy on April 21, 2017.¹³⁴ Anti-estrogen agents, including letrozole, are known to cause or contribute to hair loss.

F. Summary of Opinions

There is no medically reliable way to attribute Ms. Durden's hair loss complaint to Taxotere alone. Moreover, Ms. Durden needed chemotherapy. A Taxotere-containing regimen was an optimal choice for her treatment. She needed to take a taxane-containing regimen to prevent recurrence most effectively. The benefits outweighed the risks for her, and she was appropriately counseled on the potential risks of chemotherapy with Taxotere.

While all chemotherapy has risks and potential complications, Ms. Durden was appropriately informed of these risks prior to choosing to undergo chemotherapy with Taxotere. The available label at the time of treatment adequately apprised medical oncologists of the risk of alopecia. I feel that the use of Taxotere for Ms. Durden's breast cancer was not only appropriate, but also associated with a good survival outcome.

Barbara Earnest

I will offer case-specific opinions regarding Ms. Earnest that are based on my review of her medical records, discovery responses, and depositions, my education, training, clinical experience, review of medical and scientific literature, and information presented at various medical forums. I will offer opinions regarding her breast cancer, treatment, and alopecia. I hold all opinions to a reasonable degree of medical or scientific certainty.

¹³² Durden Dep. 44:2-5.

¹³³ Ochsner Health System 2951-2953.

¹³⁴ Ochsner Health System 2341-2352; Ochsner Medical Center 1203-1222.

Mrs. Barbara Earnest is a 68-year-old Caucasian female with a medical history of arthritis, intermittent abnormal liver enzymes, pre-diabetes, lung and splenic granulomatous disease, and morbid obesity (BMI of 42). In addition, she has a family history of diabetes and coronary artery disease in first and second-generation family members.

Ms. Earnest was diagnosed with invasive ductal breast cancer in 2011 at 60 years of age. Ms. Earnest's breast cancer was ER+, PR+, and HER2-. She had one lymph node that tested positive for cancer.

Ms. Earnest needed surgery, and had a lumpectomy.¹³⁵ Because Ms. Earnest had a lumpectomy, she needed radiation. Ms. Earnest also needed chemotherapy.

A. Taxotere Had Advantages Over Paclitaxel, Which Would Have Been More Likely to Worsen Her Neuropathy

After surgery, Ms. Earnest consulted with a medical oncologist, Dr. James Carinder, who recommended chemotherapy.¹³⁶ Dr. Carinder recommended four cycles of dose-dense doxorubicin and cyclophosphamide, followed by four cycles of docetaxel given every 21 days.¹³⁷

Dr. Carinder testified that he preferred using docetaxel over paclitaxel.¹³⁸ At the time Ms. Earnest was being treated, paclitaxel was given at a "high dose every two weeks or three weeks...."¹³⁹ And paclitaxel often resulted in "daunting" neuropathy for patients.¹⁴⁰ Dr. Carinder preferred docetaxel over paclitaxel because docetaxel had a lower risk of neuropathy and infusion reactions.¹⁴¹

Dr. Carinder made an appropriate decision in recommending docetaxel over paclitaxel for Ms. Earnest. The risk of developing such neuropathy is something that Ms. Earnest would have wanted to know before deciding to take a Taxol-containing regimen.¹⁴² This is true irrespective of changes made by oncologists in how they administer Taxol, by frequency or by dose.

Neuropathy was, and continues to be, a major risk with patients taking paclitaxel. But in patients like Ms. Earnest, who are at a higher risk of developing debilitating permanent neuropathy, paclitaxel is a less attractive option. Because of the risk of neuropathy with

¹³⁵ LSU Bogalusa Medical Center 29–30; LSU Bogalusa Medical Center 35–39.

¹³⁶ Northshore Oncology Associates, at 233, 222–224.

¹³⁷ Northshore Oncology Associates, at 233, 222–224.

¹³⁸ James Carinder Dep. 26:8–8.

¹³⁹ James Carinder Dep. 129:31.

¹⁴⁰ James Carinder Dep. 26:8–8; 69:6–19; 130:2.

¹⁴¹ James Carinder Dep. 26:8–8; 26:18–25; 69:6–19.

¹⁴² Barbara Earnest Dep. 109:7–18; 111:1–25; 112:1–9.

Taxol, Ms. Earnest's previous history with shingles, and a significant family history of diabetes, docetaxel was a good choice.

Diabetics are at a higher risk of developing neuropathy.¹⁴³ Ms. Earnest testified that her mother and father both died of complications from diabetes and that four of her siblings have been diagnosed with the disease.¹⁴⁴ Her medical records demonstrate that she is pre-diabetic, and was diagnosed with diabetes during chemotherapy.¹⁴⁵

Ms. Earnest has neuropathy to this day and continues to take Gabapentin to treat it.¹⁴⁶ Her neuropathy may have been worse if she had received a Taxol-containing regimen.

Barbara Earnest has a strong family history for heart disease and diabetes in first and second generation family members.¹⁴⁷

I believe that Ms. Earnest was an appropriate candidate for chemotherapy with Taxotere. The benefits outweighed the risks for her, and she was appropriately counseled on the potential risks of chemotherapy with Taxotere.

B. The Risk of Hair Loss With Chemotherapy is Labelled

In 2011, the FDA-approved label for Adriamycin included that "Patients should be informed that they will almost certainly develop alopecia." It continued: "The most common side effects of Doxorubicin include: hair loss (alopecia). Your hair may re-grow after your treatment." Under cutaneous reactions, the label reads "Reversible complete alopecia occurs in most cases."

In 2011, the FDA-approved label for cyclophosphamide included "Adverse Reactions," reading that "Adverse reactions reported most often include neutropenia, febrile neutropenia, fever, alopecia, nausea, vomiting, and diarrhea." Under common adverse reactions, the label lists "skin and its structure" reactions: "Alopecia occurs in patients treated with cyclophosphamide."

In 2011, the FDA-approved label for Taxotere included "Adverse Reactions," reading that "[t]he most common adverse reactions across all TAXOTERE indications are...alopecia."¹⁴⁸ Information on alopecia was included in various other parts of the label.¹⁴⁹ In the Patient Counseling Information section it stated: "Explain to patients that

¹⁴³ Slidell Memorial Hospital 239-41.

¹⁴⁴ Barbara Earnest Dep. 107:25; 108:1-19; Barbara Earnest Dep. 109:20-21; Barbara Earnest Dep. 137:6-11.

¹⁴⁵ PPR 1625-26; Bruce Samuels 22-23.

¹⁴⁶ PPR 4543-4573.

¹⁴⁷ Slidell Memorial Hospital 239-241.

¹⁴⁸ Taxotere (05/2010).

¹⁴⁹ Taxotere (05/2010).

side effects such as... hair loss are associated with docetaxel administration.”¹⁵⁰ And in the Patient Information section the label stated: “The Most common side effects of TAXOTERE include: ... hair loss.”¹⁵¹

The Taxotere label that Dr. Carinder would have read stated in the Patient Information Leaflet: “Hair Loss – Loss of hair occurs in most patients taking Taxotere (including the hair on your head, underarm hair, pubic hair, eyebrows, and eyelashes). Hair loss will begin after the first few treatments and varies from patient to patient. Once you have completed all your treatment, hair generally grows back. Your doctor or nurse can refer you to a store that carries wigs, hairpieces, and turbans for patients with cancer.”¹⁵²

Dr. Carinder testified that he read the package insert (or labeling) for Taxotere “back when it went on the market,” before the year 1999 or 2000.¹⁵³ Once again, the label, or changes to the label, make no significant difference in prescribing decisions or patient counseling when they are not read or consulted.

C. Awareness of Rare Risk of Permanent or Persistent Hair Loss with Chemotherapy

Dr. Carinder suggested that he did not know of the risk of permanent or persistent hair loss at the time of Ms. Earnest’s treatment.¹⁵⁴ However, Dr. Carinder’s testimony seems premised on the belief that there is a permanent hair loss risk carried by Taxotere that is common, proven, or unacceptably high. Dr. Carinder did know of the possibility that his patients taking dose-dense A/C followed by Taxol could develop permanent hair loss. He knew of this as a reality because he had already had a patient six years earlier that had developed persistent or permanent hair loss on that regimen.¹⁵⁵

Dr. Carinder explicitly chose not to warn patients about such a risk at the outset because, in his experience, it was exceedingly rare. Dr. Carinder has treated hundreds of breast cancer patients over the course of his career.¹⁵⁶ In that time, he has only seen two patients whose hair did not regrow as expected, which he believes may have been caused by chemotherapy.¹⁵⁷

It is common for an oncologist not to mention non-life-threatening and rare risks to patients – even if the oncologist has seen it firsthand. Oncologists have a difficult job of educating patients about their treatment options while reassuring them on the possibilities of success

¹⁵⁰ Taxotere (05/2010).

¹⁵¹ Taxotere (05/2010).

¹⁵² Taxotere Label (05/1996).

¹⁵³ James Carinder Dep. 119:3-14.

¹⁵⁴ James Carinder Dep. 27:4-9.

¹⁵⁵ James Carinder Dep. 182:9-13; James Carinder Dep. 124:17-19; James Carinder Dep. 86:3-6.

¹⁵⁶ James Carinder Dep. 61:13-25; 62:1-7.

¹⁵⁷ James Carinder Dep. 85:2-12.

and providing hope that the patient will survive.¹⁵⁸

Dr. Carinder testified that it is not reasonable or appropriate to cover all labeled risks with patients.¹⁵⁹ Dr. Carinder testified that he warns his patients about the most common side effects. And he always warns about the unknowns with chemotherapy.¹⁶⁰

Dr. Carinder does not recall what he specifically said to Ms. Earnest other than that her hair would fall out.¹⁶¹ Still, he similarly testified that, when asked about permanent hair loss, he told patients that he had one patient whose hair did not regrow.¹⁶² Dr. Carinder typically does not tell his patients that their hair will absolutely regrow.¹⁶³

Ms. Earnest's husband, Ralph, was at the appointment with Dr. Carinder.¹⁶⁴ He remembers Dr. Carinder telling them that "it was possible [her hair] would never grow back."¹⁶⁵

In addition, before ever meeting with an oncologist, Ms. Earnest saw a surgeon regarding her cancer treatment, Dr. Celeste LeGarde. Dr. LeGarde left Ms. Earnest a copy of the pathology report and an educational breast cancer book.¹⁶⁶ The book provided by Dr. LeGarde in February 2011 is titled: "Breast Cancer Treatment Handbook."¹⁶⁷ The book specifically states that there have been "rare reports of permanent hair loss" with Taxotere (docetaxel).¹⁶⁸

On March 31, 2011, Barbara Earnest signed a chemotherapy informed consent that warned of side effects from chemotherapy, including hair loss, death, brain damage, quadriplegia, paraplegia, loss of organ function, loss of an arm, and loss of a leg.¹⁶⁹ In addition, in the form, Ms. Earnest acknowledge that, "I understand there is a risk of very uncommon, rare, or previously unknown side effects developing because of the use of these drugs."¹⁷⁰

Ms. Earnest understood and agreed to the risk of hair loss.¹⁷¹ She understood and agreed to the risk of bleeding or anemia.¹⁷² She understood and agreed to the risk of potentially life threatening damage to such vital organs as the heart, lungs, liver and kidneys.¹⁷³ She

¹⁵⁸ James Carinder Dep. 88:24.

¹⁵⁹ James Carinder Dep. 87:25; 88:1-25; 89:1-6.

¹⁶⁰ James Carinder Dep. 19-23.

¹⁶¹ James Carinder Dep. 115:16-116:14.

¹⁶² James Carinder Dep. 125:4-12.

¹⁶³ James Carinder Dep. 96:13-16.

¹⁶⁴ Ralph Earnest Dep. 146:21-25.

¹⁶⁵ Ralph Earnest Dep. 147:24-148:13.

¹⁶⁶ Celeste LeGarde at 22.

¹⁶⁷ PPR at 001760, Ex. 3, Celeste LeGarde Dep. 57:6-8.

¹⁶⁸ PPR 001972.

¹⁶⁹ Northshore Oncology Associates 315-16.

¹⁷⁰ Northshore Oncology Associates 315-16.

¹⁷¹ Barbara Earnest Supp. Dep. 34-36.

¹⁷² Barbara Earnest Supp. Dep. 34-36.

¹⁷³ Barbara Earnest Supp. Dep. 34-36.

understood and agreed to the risk of losing an organ.¹⁷⁴ She understood and agreed to the risk of losing a limb.¹⁷⁵ She understood and agreed to the risk of losing function of an organ.¹⁷⁶ Ms. Earnest understood and agreed to the risk of quadriplegia.¹⁷⁷ She understood and agreed to the risk of paraplegia. She understood and agreed to the risk of brain damage.¹⁷⁸ She accepted all of these risks.¹⁷⁹

Ms. Earnest specifically understood that there was a risk of unknowns with chemotherapy.¹⁸⁰ She accepted these risks because she wanted to give herself the best chance of survival.¹⁸¹

Ms. Earnest was appropriately informed of the risks and possible complications before choosing to undergo chemotherapy with Taxotere, and she determined the benefits outweighed those risks. The available label at the time of treatment adequately apprised medical oncologists of the risk of alopecia. Based on his own clinical experience, Dr. Carinder was aware of another patient with alopecia after chemotherapy. Dr. Carinder warned Ms. Earnest of the risk of developing unknown or rare side effects, including a specific warning that he was aware of a case of persistent or permanent hair loss.

D. Ms. Earnest Took A/C and Experienced Total Hair Loss Before Taking Taxotere

Every three weeks, Ms. Earnest went in for chemotherapy.¹⁸² She underwent chemotherapy eight times.¹⁸³ The first four times, she received two medicines – doxorubicin and cyclophosphamide.¹⁸⁴ The next four times, she received one other medicine – docetaxel.¹⁸⁵ Ms. Earnest experienced total hair loss following the administration of doxorubicin and cyclophosphamide. It is impossible to single out Taxotere as the cause of Ms. Earnest's alopecia when she lost her hair well before taking the medicine, while on two other chemotherapy agents.

E. Ms. Earnest's Course of Care Following Chemotherapy Included Radiation

¹⁷⁴ Barbara Earnest Supp. Dep. 34–36.

¹⁷⁵ Barbara Earnest Supp. Dep. 34–36.

¹⁷⁶ Barbara Earnest Supp. Dep. 34–36.

¹⁷⁷ Barbara Earnest Supp. Dep. 34–36.

¹⁷⁸ Barbara Earnest Supp. Dep. 34–36.

¹⁷⁹ Barbara Earnest Supp. Dep. 34–36.

¹⁸⁰ Barbara Earnest Supp. Dep. 41:2–5; Northshore Oncology Associates, 315–16.

¹⁸¹ Barbara Earnest Supp. Dep. 39:24–25; 40:1–5.

¹⁸² Plaintiff Fact Sheet § V.12.

¹⁸³ Slidell Memorial Hospital 261–67; Slidell Memorial Hospital 293–304; Slidell Memorial Hospital 333–341; Slidell Memorial Hospital 377–84; Slidell Memorial Hospital 426–33; Slidell Memorial Hospital 478–85; Slidell Memorial Hospital 527–38; Slidell Memorial Hospital 600–10.

¹⁸⁴ Plaintiff Fact Sheet § V.12.a; Slidell Memorial Hospital 261–67; Slidell Memorial Hospital 293–304; Slidell Memorial Hospital 333–341; Slidell Memorial Hospital 377–84.

¹⁸⁵ Plaintiff Fact Sheet § V.12.a; Slidell Memorial Hospital 426–33; Slidell Memorial Hospital 478–85; Slidell Memorial Hospital 527–38; Slidell Memorial Hospital 600–10.

Ms. Earnest received radiation treatment between October 3, 2011 and November 21, 2011.¹⁸⁶

F. Ms. Earnest's Course of Care After Chemotherapy Included Hormonal Treatment

Ms. Earnest started hormone therapy (Arimidex) in November 2011.¹⁸⁷ Dr. Carinder recommended Arimidex because of the hormone positive status of her cancer.¹⁸⁸ Patients of Dr. Carinder have experienced significant hair thinning from Arimidex.¹⁸⁹ Dr. Carinder tells patients that “Not every patient gets thinning of the hair” with Arimidex.¹⁹⁰

In 2015, Ms. Earnest saw Dr. Moehlen at the Tulane Liver Clinic to follow up on abnormal liver chemistries.¹⁹¹ Her bilirubin was slightly elevated at 1.2 in November 2013 and 2.0 in September 2014.¹⁹² She was told she has fatty liver disease and that she might need a biopsy at some point.¹⁹³ Dr. Moehlen noted that Arimidex “can cause elevations in GGT and alkaline phosphatase [largely thought to be due to bone isoforms of the enzymes], however, there have been no convincing reports of hepatotoxicity in the medical literature related to this.”¹⁹⁴ Dr. Moehlen discussed the possibility of “drug-induced liver injury” caused by Arimidex with Ms. Earnest.¹⁹⁵ Dr. Moehlen, however, told Ms. Earnest to continue taking Arimidex because “the benefits of the drug outweigh the potential harm.”¹⁹⁶

In December 2016, after five years of taking Arimidex, Ms. Earnest again discussed the risks and benefits of continuing hormone therapy with her new oncologist, Dr. Collins-Burrow.¹⁹⁷ Ms. Earnest opted to continue hormone therapy to lower the risk of recurrence.¹⁹⁸ She continues to take Arimidex.

G. Summary

Ms. Earnest needed chemotherapy. A Taxotere-containing regimen was an appropriate

¹⁸⁶ Slidell Radiation Center 23–25; Slidell Radiation Center 15–22.

¹⁸⁷ Northshore Oncology Associates 251–52.

¹⁸⁸ Northshore Oncology Associates 233, 222–224.

¹⁸⁹ James Carinder Dep. 110:14–16.

¹⁹⁰ James Carinder Dep. 114:22–25; 115:1–8.

¹⁹¹ Tulane Liver Clinic 291–98.

¹⁹² Tulane Liver Clinic 291–98.

¹⁹³ Tulane Liver Clinic 291–98.

¹⁹⁴ Tulane Liver Clinic 291–98.

¹⁹⁵ Tulane Liver Clinic 291–98.

¹⁹⁶ Tulane Liver Clinic 291–98.

¹⁹⁷ Tulane Medical Center 12–16; Tulane Cancer Center 134–41.

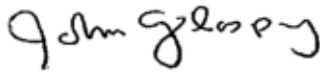
¹⁹⁸ Tulane Medical Center 12–16; Tulane Cancer Center 134–41; Barbara Earnest Depo. 226:8–11, 290:16–18; Slidell Radiation Center 5–7.

choice for her treatment. She needed to take a taxane-containing regimen to optimally prevent recurrence. It was reasonable to avoid Taxol because of the risk of neuropathy. Ms. Earnest has not had a relapse of her cancer.

Ms. Earnest lost her hair before chemotherapy with Taxotere. There is no medically reliable way to trace Taxotere as the significant cause of her complaints about her hair not re-growing since her pre-Taxotere chemotherapy. She voluntarily continues to take medications, including Gabapentin and Arimidex, which can cause hair loss. She is also post-menopausal, ageing, and has several other medical conditions that could contribute to her hair loss.

Before prescribing Ms. Earnest Taxotere, Dr. Carinder was aware there was a rare risk of persistent hair loss with an “AC – Taxotere” regimen, through his own clinical experience. Additionally, Dr. Carinder did not rely on Taxotere’s label when informing Ms. Earnest about side effects – he had not referenced the label in over ten years.¹⁹⁹

Ms. Earnest accepted the very serious risks of chemotherapy treatment, including rare or unknown side effects, to optimize her survival. No one could say that Ms. Earnest’s hair wouldn’t be in the same condition if she had been prescribed paclitaxel.²⁰⁰



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¹⁹⁹ James Carinder Dep. 119:3-14.

²⁰⁰ James Carinder Dep. 138:23-139:5.

Figure A – Ex. A to Sanofi’s Responses to Plaintiffs’ Notice of 30(b)(6) Deposition - Table of TAX316 Patients

Subject ID	Treatment Arm	Last Chemotherapy Treatment	Last Documentation of Ongoing Alopecia	Documented Ongoing Alopecia >6 Months	Date of Resolution	Description
11738	TAC	4/27/99	8/23/99	No	N/A	Received 5 cycles of TAC, last cycle administered 4/27/99. [Sanofi_02649521, p.7131] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.14989] After this cycle, the patient refused further treatment and withdrew her consent. [Sanofi_02649521, p.31091] During a follow up visit on 8/23/99, alopecia was recorded as ongoing. [Sanofi_02649521, p.14990, 32450] She was not seen again for follow up due to her withdrawal of consent. [Sanofi_02649521, p.32450]
12211	TAC	11/4/98	8/12/98	No	11/4/98	Received 5 cycles of TAC, last cycle administered 8/12/98. [Sanofi_02649521, p.7291] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.17558] After this cycle, the patient refused further treatment and withdrew her consent. [Sanofi_02649521, p.458, 31116] She received FAC for her 6 th cycle of treatment on 11/4/98. [Sanofi_02649521, p.458, 17559, 32793] On this date, alopecia was recorded as resolved. [Sanofi_02649521, p.17559, 32793] Alopecia was not recorded as an adverse event at any of her next 13 follow up visits. [Sanofi_02649521, p.17559, 32794-5]
12314	TAC	4/22/99	3/13/99	No	4/22/99	Received 3 cycles of TAC, last cycle administered 2/18/99. [Sanofi_02649521, p.7169-70] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_05497867] She was withdrawn from the study after developing febrile neutropenia during her 3 rd cycle of TAC and received FAC for her final 3 cycles. [Sanofi_02649521, p.335] During her 2 nd cycle of FAC on 3/13/99, alopecia was recorded as

						ongoing. [Sanofi_05497797, 05497888, 05497892] Her last cycle of FAC was administered on 4/22/99, and on this date alopecia was recorded as ceased. [Sanofi_05497898, 05497902] Alopecia was not recorded as an adverse event during any of her next 12 follow up visits. [Sanofi_05497908-66, Sanofi_02649521, p.32543-4]
12403	TAC	12/11/98	12/11/98	No	1/99	Received 6 cycles of TAC, last cycle administered 12/11/98. [Sanofi_02649521, p.7098-9] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.14379] At her first follow up visit on 4/7/99, alopecia was recorded as resolved, with 1/99 listed as the resolution date. [Sanofi_02649521, p.14380, 32374] Alopecia was not recorded as an adverse event during any of her next 10 follow up visits. [Sanofi_02649521, p.14380-2, 32374-5]
12612	TAC	5/11/99	6/12/01	Yes	12/18/01	Received 6 cycles of TAC, last cycle administered 5/11/99. [Sanofi_02649521, p.7301] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.17755] Alopecia was recorded as ongoing at her first eight follow up visits (8 th follow up on 6/12/01) [Sanofi_02649521, p.17756-9, 32760] At her ninth follow up visit on 12/18/01, alopecia was recorded as resolved and was not recorded as an adverse event at any of her next 3 follow up visits. [Sanofi_02649521, p.17759, 32818-9]
13605	TAC	8/26/98	8/26/98	No	12/3/98	Received 6 cycles of TAC, last cycle administered 8/26/98. [Sanofi_02649521, p.7486-7] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.19487] At her first follow up visit on 12/3/98, alopecia was recorded as resolved. [Sanofi_02649521, p.19488, 33177] Alopecia was not recorded as an adverse event during any of her next 13 follow up visits. [Sanofi_02649521, p.19488-9, 33177-8]
13607	TAC	9/16/98	9/16/98	No	11/23/98	Received 6 cycles of TAC, last cycle administered 9/16/98. [Sanofi_02649521, p.7487-8] On this date, the patient was

						recorded as having ongoing alopecia. [Sanofi_02649521, p.7488, 19492] At her first follow up visit on 11/23/98, alopecia was recorded as resolved. [Sanofi_02649521, p.19492, 33179] Alopecia was not recorded as an adverse event at any of her next 11 follow up visits. [Sanofi_02649521, p.33179-80]
13610	TAC	4/6/99	4/6/99	No	7/22/99	Received 6 cycles of TAC, last cycle administered 4/6/99. [Sanofi_02649521, p.7490] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.19497] At her first follow up visit on 7/22/99, alopecia was recorded as resolved. [Sanofi_02649521, p.19497, 33182] Alopecia was not recorded as an adverse event at any of her next 11 follow up visits. [Sanofi_02649521, p.19497, 33182-3]
13615	TAC	6/15/99	6/15/99	No	11/5/99	Received 6 cycles of TAC, last cycle administered 6/15/99. [Sanofi_02649521, p.7492] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.19506] At her first follow up visit on 11/5/99, alopecia was recorded as resolved. [Sanofi_02649521, p.19507, 33186] Alopecia was not recorded as an adverse event at any of her next 8 follow up visits. [Sanofi_02649521, p.19507, 33186-7]
15002	TAC	9/23/98	11/3/98	No	N/A	Received 1 cycle of TAC, administered on 8/26/98. [Sanofi_05503622; Sanofi_02649521, p.7383] The patient developed alopecia after this treatment cycle. [Sanofi_05503627] She was withdrawn from the study after developing gastrointestinal mucositis following TAC administration. [Sanofi_02649521, p.343] On 9/23/98, the patient began alternative chemotherapy treatment with AC (number of cycles received unknown). [Sanofi_05503640] At her first follow up visit on 11/3/98, alopecia was recorded as ongoing and “No longer followed due to new chemotherapy regimen started.” [Sanofi_05503639,

						05503641] No further alopecia assessments were made for this patient. After a distant breast cancer relapse, the patient began treatment with Taxol on 8/31/99. [Sanofi_05503649] She was lost to follow up since 12/22/99 [Sanofi_05503594], and recorded as deceased due to breast cancer on an unknown day in 8/01. [Sanofi_05503655]
15006	TAC	1/12/99	2/23/99	No	N/A	Received 1 cycle of TAC, administered on 12/23/98. [Sanofi_05503696; Sanofi_02649521, p.7384] The patient developed alopecia after this treatment cycle. [Sanofi_05503700] She was withdrawn from the study after developing anaphylaxis during TAC administration. [Sanofi_002649521, p.344] On 1/12/99 the patient began alternative chemotherapy treatment with AC (number of cycles received unknown). [Sanofi_05503707] At her first follow up visit on 2/23/99, alopecia was recorded as ongoing and “No longer followed due to new chemotherapy regimen started.” [Sanofi_05503711, 05503716] No further alopecia assessments were made for this patient. After a distant breast cancer relapse, the patient began treatment with vinorelbine on 8/10/99. [Sanofi_05503719]
15606	TAC	12/4/98	1/11/99	No	N/A	Received 6 cycles of TAC, last cycle administered 12/4/98. [Sanofi_02649521, p.7398-9] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.18545] At her first follow up visit on 1/11/99, alopecia was recorded as ongoing. [Sanofi_02649521, p.18545, 33002] No further assessments of alopecia were made for this patient. On 7/25/01, the patient was described as lost to follow up. [Sanofi_02649521, p.33002]
15808	TAC	9/4/98	12/30/98	No	N/A	Received 6 cycles of TAC, last cycle administered 9/4/98. [Sanofi_02649521, p.7337] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.18077] At her first follow up visit on 12/30/98, she was diagnosed with a breast cancer relapse. [Sanofi_02649521,

						p.539] On this date, alopecia was recorded as ongoing and no longer followed. [Sanofi_02649521, p.18078] No further alopecia assessments were made for this patient.
17603	TAC	5/8/98	2/19/99	Yes	5/7/99	Received 6 cycles of TAC, last cycle administered 5/8/98. [Sanofi_02649521, p.7661] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.20652] Alopecia was recorded as ongoing during her first three follow-up visits (3 rd follow up on 2/19/99). [Sanofi_02649521, p.20653, 33545] At her fourth follow up visit on 5/7/99, alopecia was listed as resolved. [Sanofi_02649521, p.20654, 33545]
17608	TAC	6/23/98	9/22/98	No	N/A	Received 2 cycles of TAC, last cycle administered 6/23/98. [Sanofi_02649521, p.7664] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.20681] After receiving her 2 nd cycle of TAC, the patient withdrew her consent and refused further treatment. [Sanofi_02649521, p.31173] On 7/14/98 the patient began alternative chemotherapy treatment with Adriamycin and Cyclophosphamide. [Sanofi_02649521, p.35363] At her first follow up visit on 9/22/98, alopecia was recorded as ongoing but no longer followed due to withdrawal of consent. [Sanofi_02649521, p.20682, 33551]
22312	TAC	5/10/99	4/19/99	No	5/10/99	Received 2 cycles of TAC, last cycle administered 2/15/99. [Sanofi_05498037; Sanofi_02649521, p.7178] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_05498037, 05498041] Due to an allergic reaction during infusion of the second cycle of TAC, the patient was withdrawn from the study and received FAC for her final 4 cycles of treatment. [Sanofi_02649521, p.360] During her 3 rd cycle of FAC administration on 4/19/99, alopecia was recorded as ongoing. [Sanofi_05498075, 05498079] Her final cycle of FAC was administered on 5/10/99. [Sanofi_05498085] Alopecia was recorded as ceased on this

						date. [Sanofi_05498089] Alopecia was not recorded as an adverse event during any of her next 11 follow-up visits [Sanofi_05498095-136]
22702	TAC	11/25/98	11/25/98	No	N/A	Received 2 cycles of TAC, last cycle administered 9/2/98. [Sanofi_02649521, p.7183-7184] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_05498537, 05498541] Due to the development of allergy and dyspnea, the patient was withdrawn from the study and received FAC for her last 4 cycles of treatment [Sanofi_02649521, p.364] Her last cycle of FAC was administered on 11/25/98, and the status of her alopecia was listed as ongoing. [Sanofi_05498596, 05498600] No further alopecia assessments were made for this patient. [Sanofi_05498606-662; Sanofi_02649521, p.15835]
23907	TAC	11/25/98	2/99	No	N/A	Received 4 cycles of TAC, last cycle administered 11/25/98. [Sanofi_02649521, p.7501] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.19573] After her 4 th cycle of TAC, the patient suffered a breast cancer relapse, and she was withdrawn from the study. [Sanofi_02649521, p.651] At her first follow up visit, alopecia was recorded as ongoing. [Sanofi_02649521, p.19573] A date for this follow up visit has not been identified. As per protocol, this visit would have been 3 months after the last chemotherapy administration (roughly 2/99). Alopecia was not recorded as an adverse event during 4 abbreviated follow up visits between 3/18/99 and 3/6/03. [Sanofi_02649521, p.19573, 33204]
25010	TAC	8/20/99	11/25/99	No	N/A	Received 4 cycles of TAC, last cycle administered 7/30/99. [Sanofi_05503801; Sanofi_02649521, p.7388-7389] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_05503805] After this cycle, she developed a serious episode of febrile neutropenia and was discontinued from the study. [Sanofi_02649521, p.368-369] On 8/20/99 she began

						alternative chemotherapy with epirubicin and cyclophosphamide (number of cycles received unknown). [Sanofi_05503819] At her first follow-up visit on 11/25/99, her alopecia status was recorded as ongoing and “No longer followed due to new chemotherapy regimen started.” [Sanofi_05503816, 05503820] No further alopecia assessments were made for this patient. [Sanofi_05503821-851]
26802	TAC	9/28/98	12/31/98	No	N/A	Received 5 cycles of TAC, last cycle administered 9/7/98. [Sanofi_05506753; Sanofi_02649521, p.7478] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_05506757] After experiencing total body anesthesia after administration of cycle 5, she was withdrawn from the study. [Sanofi_02649521, p.372] On 9/28/98 she began alternative chemotherapy with AC (number of cycles received unknown). [Sanofi_05506765] At her first follow-up visit on 12/31/98, her alopecia status was recorded as ongoing and “No longer followed due to new chemotherapy regimen started.” [Sanofi_05506769-70] No further alopecia assessments were made for this patient.
29701	TAC	8/14/98	11/12/98	No	N/A	Received 3 cycles of TAC, last cycle administered 7/9/98. [Sanofi_05468927; Sanofi_02649521, p.7697] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_05468931] After repeated episodes of neutropenia with each chemotherapy cycle, she was withdrawn from the study. [Sanofi_02649521, p.380, Sanofi_05468940] On 8/14/98 she began alternative chemotherapy with AC (number of cycles received unknown). [Sanofi_05468939] At her first follow-up visit on 11/12/98, her alopecia status was recorded as ongoing and “No longer followed due to new chemotherapy regimen started.” [Sanofi_05468942-3] No further alopecia assessments were made for this patient. [Sanofi_05468944-982]

30702	TAC	4/16/99	4/16/99	No	8/30/99	Received 6 cycles of TAC, last cycle administered 4/16/99. [Sanofi_02228520; Sanofi_02649521, p.7765] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02228524] At her first follow up visit on 8/30/99, alopecia was recorded as resolved. [Sanofi_02228538, 02228542, Sanofi_02649521, p.21823, 33792] Alopecia was not recorded as an adverse event at any of her next 11 follow up visits. [Sanofi_02228543-02228587, Sanofi_02649521, p.33792-3]
40401	TAC	8/3/98	9/22/98	No	N/A	Received 3 cycles of TAC, last cycle administered 7/2/98. [Sanofi_03244422; Sanofi_02649521, p.7768] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_03244427] After episodes of febrile neutropenia with each TAC cycle [Sanofi_02649521, p.387], the patient refused further treatment stating she “didn’t want any more of this treatment,” and she was discontinued from the study. [Sanofi_03244442] On 8/3/98 she began alternative chemotherapy treatment with AC (number of treatment cycles unknown). [Sanofi_03244450] At her first follow-up visit on 9/22/98, her alopecia status was recorded as ongoing and “No longer followed due to new chemotherapy regimen started.” [Sanofi_03244444, 03244449, 03244562-3] No further alopecia assessments were made for this patient. [Sanofi_03244451-454; Sanofi_02649521, p.21862-21864]
13608	FAC	1/18/99	1/18/99	No	4/22/99	Received 6 cycles of FAC, last cycle administered on 1/18/99. [Sanofi_02649521, p.8221] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.19494] At her first follow up visit on 4/22/99, her alopecia status was recorded as resolved. [Sanofi_02649521, p.19494, 33180]
16301	FAC	3/11/99	5/26/99	No	N/A	Received 3 cycles of FAC, last cycle administered on 1/28/99. [Sanofi_02649521, p.8147] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521,

						p.18688; Sanofi_05511537] Following this cycle, the patient developed fever and tiredness due to grade 4 bacteremia. She was withdrawn from the study because the investigator felt her health was not strong enough. [Sanofi_02649521, p.736]. On 3/11/99 she began alternative treatment with CMF chemotherapy (number of treatment cycles unknown). [Sanofi_02649521, p.736; Sanofi_05511551] At her first follow-up visit on 5/26/99, her alopecia status was recorded as ongoing and “No longer followed due to new chemotherapy regimen started.” [Sanofi_02649521, p.18689; Sanofi_05511550] No further alopecia assessments were made for this patient. [Sanofi_05511556-626; Sanofi_02649521, p.18689]
19801	FAC	3/17/98	3/17/98	No	5/12/98	Received 6 cycles of FAC, last cycle administered on 3/17/98. [Sanofi_02218444; Sanofi_02649521, p.8461] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.21339; Sanofi_02218448] At her first follow up visit on 7/14/98, alopecia was recorded as resolved, with a resolution date of 5/12/98. [Sanofi_02218341]
20610	FAC	4/29/99	7/8/99	No	N/A	Received 6 cycles of FAC, last cycle administered on 4/29/99. [Sanofi_02649521, p.7961] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.16574] On 5/31/99 she was diagnosed with breast cancer relapse, and she began alternative anti-cancer treatment, the details of which were not provided to investigators. [Sanofi_02649521, p.938] At her first follow up visit on 7/8/99, alopecia was recorded as ongoing. [Sanofi_02649521, p.16575, 32662; Sanofi_05501313] The patient died of breast cancer on 8/30/99. [Sanofi_02649521, p.938; Sanofi_05501314]
24411	FAC	3/10/99	6/10/99	No	N/A	Received 6 cycles of FAC, last cycle administered on 3/10/99. [Sanofi_05476972; Sanofi_02649521, p.8292] On

						this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.20002; Sanofi_05476976] On 6/9/99 the patient was diagnosed with breast cancer relapse. [Sanofi_02649521, p.965; Sanofi_05476994] At her first follow up visit on 6/10/99, alopecia was recorded as ongoing and “No longer followed due to new chemotherapy regimen started.” [Sanofi_02649521, p.20002, 33350; Sanofi_05476993] She began treatment with alternative navelbine chemotherapy on 6/11/99. [Sanofi_02649521, p.965; Sanofi_05476995] No further alopecia assessments were made for this patient. [Sanofi_05476997; Sanofi_02649521, p.20002-3]
24520	FAC	2/11/99	3/22/99	No	N/A	Received 6 cycles of FAC, last cycle administered on 2/11/99. [Sanofi_02649521, p.8342] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.20363] On 3/22/99 the patient was diagnosed with breast cancer relapse. [Sanofi_02649521, p.33458, 35222] Also on 3/22/99, her alopecia status was recorded as ongoing and no longer followed due to new chemotherapy regimen started. [Sanofi_02649521, p.20363, 33458] She began alternative Taxotere chemotherapy on 4/7/99. [Sanofi_02649521, p.35351] No further alopecia assessments were made for this patient. [Sanofi_02649521, p.20363]
25501	FAC	11/16/98	2/12/99	No	N/A	Received 6 cycles of FAC, last cycle administered on 11/16/98. [Sanofi_02649521, p.8085] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.18221] She was diagnosed with breast cancer relapse on 1/1/01. [Sanofi_02649521, p.32918, 35195] At her first follow up visit on 2/12/99, her alopecia status was recorded as ongoing and no longer followed due to alternative anti-cancer therapy she was receiving. [Sanofi_02649521, p.18221, 35309] No further alopecia

						assessments were made for this patient. [Sanofi_02649521, p.18221]
25601	FAC	4/3/98	9/14/98	No	N/A	Received 6 cycles of FAC, last cycle administered on 4/3/98. [Sanofi_02649521, p.8130] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.18552; Sanofi_05506268] She was diagnosed with breast cancer relapse on 9/14/98. [Sanofi_02949521, p.33003; Sanofi_05506286] Also on 9/14/98, her alopecia status was recorded as ongoing and “no longer followed due to new chemotherapy regimen started.” [Sanofi_02649521, p.18552, Sanofi_05506285] She began alternative Taxotere chemotherapy on 9/19/98. [Sanofi_02649521, p.974; Sanofi_05506287] No further alopecia assessments were made for this patient. [Sanofi_05506287-9; Sanofi_02649521, p.18552]
26804	FAC	11/18/98	11/18/98	No	3/16/99	Received 6 cycles of FAC, last cycle administered on 11/18/98. [Sanofi_05506403; Sanofi_02649521, p.8210] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.19416; Sanofi_05506407] At her first follow up visit on 3/16/99, her alopecia status was recorded as resolved. [Sanofi_02649521, p.19417; Sanofi_05506423]
27304	FAC	8/9/99	9/7/99	No	N/A	Received 6 cycles of FAC, last cycle administered on 8/9/99. [Sanofi_05466953; Sanofi_02649521, p.8494] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.21744; Sanofi_05466960] At her first follow up visit on 9/7/99, her alopecia status was recorded as ongoing. [Sanofi_02649521, p.21746; Sanofi_05466960] On that same day (9/7/99), she was diagnosed with breast cancer relapse. [Sanofi_02649521, p.815, 35239; Sanofi_05466978] On 9/15/99, the patient died after developing thrombosis, hepato-renal failure, and acute respiratory failure. [Sanofi_02649521, p.815]

27601	FAC	8/7/98	9/8/98	No	N/A	Received 6 cycles of FAC, last cycle administered on 4/17/98. [Sanofi_02649521, p.8390-91] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.20736] For an unknown reason (but presumably due to a breast cancer relapse), on 8/7/98 the patient began alternative high-dose chemotherapy (cyclophosphamide, carboplatin, thiotepa) with autologous peripheral stem cell support. [Sanofi_02649521, p.33559, 35364] At her first follow up visit on 9/8/98, her alopecia status was recorded as ongoing and no longer followed due to alternative anti-cancer therapy regimen started. [Sanofi_02649521, p.20736] No further alopecia assessments were made for this patient. [Sanofi_02649521, p.20736]
27610	FAC	9/10/99	3/3/00	No	6/16/00	Received 6 cycles of FAC, last cycle administered on 9/10/99. [Sanofi_02649521, p.8396] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.20790] At her first and second follow up visits on 12/2/99 and 3/3/00, respectively, her alopecia status was recorded as ongoing. [Sanofi_02649521, p.20791, 33568] At her third follow up visit on 6/16/00, her alopecia status was recorded as resolved. [Sanofi_02649521, p.20792, 33569]
32207	FAC	5/26/99	9/15/99	No	N/A	Received 6 cycles of FAC, last cycle administered on 5/26/99. [Sanofi_02649521, p.7798] On this date, the patient was recorded as having ongoing alopecia. [Sanofi_02649521, p.14163] At her first follow up visit on 9/15/99, her alopecia status was recorded as ongoing. [Sanofi_02649521, p.14164, 32309] During her next 11 follow up visits through 6/25/03, alopecia was not listed as resolved but was also not listed as an adverse event. [Sanofi_02649521, p.14164, 32309-10]

EXHIBIT L

Filed Under Seal

EXHIBIT L

**EXPERT REPORT OF JANET B. ARROWSMITH, M.D., F.A.C.P, F.A.C.E.
IN RE TAXOTERE (DOCETAXEL) PRODUCTS LIABILITY LITIGATION
SUBMITTED DECEMBER 31, 2018**

I. BACKGROUND

1. I earned my undergraduate degree in zoology from Duke University in 1972 and my medical degree in 1979 from Tulane University School of Medicine.

2. I am board-certified in Internal Medicine and licensed to practice medicine in the State of New Mexico. I am an epidemiologist, trained through the Epidemic Intelligence Service (EIS) of the U.S. Centers for Disease Control and Prevention (CDC). I am an elected Fellow of the American College of Physicians and an elected Fellow of the American College of Epidemiology.

3. As part of the CDC training, I was assigned to the postmarket safety surveillance division of the U.S. Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER). As an EIS officer and later as an FDA medical epidemiologist and medical officer, I received training and experience in the application of the laws and regulations that govern the pre-market development, review, approval, labeling and postmarket safety review for pharmaceutical products intended for the U.S. market. I became very familiar with FDA's practices in the review, approval, and labeling of drugs intended for the U.S. market. My training and experience through the CDC program and at FDA provided me with the skills and knowledge necessary to practice pharmacoepidemiology, a subspecialty of the science of epidemiology having to do with assessing the safety of marketed pharmaceutical products.

4. The CDC training program encompassed two years from July 1, 1984 through June 30, 1986, during which I received training in food, drug, biological product and medical

device laws and regulations. Following completion of my training program, I was hired as a medical epidemiologist in the Office of Epidemiology and Biostatistics at CDER. The work I did at CDER from 1984-1988 resulted in numerous labeling changes for pharmaceutical products available on the U.S. market. My additional experience at FDA included serving from 1988-1990 as Deputy Director of the program known as the Office of Special Health Issues within the Office of the Commissioner of FDA. This Office was previously known as the AIDS Coordination Staff and then Office of AIDS and Special Health Issues. From 1991-1993, I also served as a Medical Review Officer in the Division of Anti-Viral Drug Products within CDER. At CDER, I reviewed Investigational New Drug Exemption Requests and a crucial portion of a New Drug Application as it related to safety and labeling for didanosine, the second antiviral drug approved in the U.S. for use in the treatment of HIV and AIDS.

5. From 1993-1995, I served as the Acting Director of the Office of Surveillance and Biometrics in the FDA Center for Devices and Radiological Health (CDRH). In that capacity, my staff and I were responsible for monitoring the safety and potential problems associated with all medical devices marketed within the U.S. as well as providing statistical support for the premarket medical device review divisions within the Office of Device Evaluation in CDRH. I was responsible for decisions affecting the continued market availability of medical devices in the U.S.

6. Following my tenure at CDRH, I chose to move from the Acting Director position in CDRH to the Center for Biologic Evaluation and Research (CBER), where I served as a Medical Review Officer in the Division of Blood and Blood Products from 1995-1996. I remained in that position until moving to New Mexico, where I was assigned as a primary care provider at the Mescalero Apache Indian Health Service Hospital. I served two years in that

position before accepting a position in 1998 as an internal medical physician with full hospital and ICU privileges at the Lincoln County Medical Center in Ruidoso, New Mexico, where I remained in full-time adult medical practice until late 1999.

7. I am a peer reviewer for the *Annals of Internal Medicine* and the *Annals of Epidemiology*. I also have been an abstract reviewer for the American College of Epidemiology, the International Society of Pharmacoepidemiology, and served on the Editorial Board for the *Journal of Pharmacoepidemiology*. I have numerous publications in the peer-reviewed literature, as well as book chapters addressing postmarket safety surveillance of medical products and outlining the legal and regulatory history of the U.S. Food and Drug Administration. I served as coauthor on a chapter entitled “A View From a Regulatory Agency” for the first two editions of the textbook “Pharmacoepidemiology”; I was sole author and then senior author for a textbook chapter addressing postmarket surveillance of medical products in the U.S. in “Principles and Practices of Public Health Surveillance.” My peer-reviewed publications generally address postmarket safety surveillance and provide the results of epidemiologic studies related to infectious diseases and potential safety issues associated with pharmaceutical products. Citations for these publications, and other information regarding my experience and qualifications, are listed in my curriculum vitae provided as Attachment A. I have lectured regularly for various continuing medical education (CME) courses around the country.

8. While serving at FDA, CDC and the Indian Health Service, I was a Commissioned Officer in the U.S. Public Health Service (USPHS), with service dates from July 1984 through February 1998, attaining the Navy rank of Captain (O-6). I received an honorable discharge in 1998. From 1986-1996, I also was a clinical instructor in the Department of Medicine at Georgetown University Medical Center in Washington, DC. Since 1999, I have

served as a consultant and independent contractor. Among other entities and organizations, I have consulted with the National Institute on Drug Abuse (NIDA), Division of Research and Development, National Institutes of Health (NIH) and the National Institute of Allergy and Infectious Diseases, NIH. My work with NIDA involved the review of investigational new drug proposals and providing recommendations for candidate products for further development by NIDA in support of its mission to reduce drug abuse in the U.S. I also served as a peer-reviewer for contract proposals submitted to NIAID and the Division of AIDS for AIDS-related therapeutic product development and for companies providing international clinical trial support in developing interventions to combat organisms with the potential for use in bioterrorism.

9. My opinions are based upon my extensive training and experience as a physician, epidemiologist and my tenure at FDA, as reflected in my curriculum vitae, which is attached as Exhibit A.

10. My opinions also are based on the documents I have reviewed and my independent research. I have reviewed a substantial number of documents concerning advertising and promotional materials. Some of the documents I reviewed are referenced in this report. I cannot cite all the materials I have ever reviewed which may support my opinions, as these would include documents, regulations, medical literature and texts that I reviewed over the course of my career and prior to my being retained by Sanofi. I may also rely on additional documents to respond to the testimony of other experts or witnesses, and supplement the opinions set forth in this report. A bibliography of some of the documents I have considered is included in Exhibit B. My testimony from the last four years is provided in Exhibit C.

11. My hourly fee for document review, testimony and other activities in this matter is \$750.00 per hour. I have testified on behalf of both defendants and plaintiffs in products

liability litigation. I hold all opinions expressed in this report to a reasonable degree of expert certainty or probability.

II. SUMMARY OF FINDINGS AND OPINIONS

- a. *Taxotere was appropriately developed and evaluated by Sanofi's predecessor manufacturer. The necessary and complete data set was provided to FDA.*
- b. *FDA thoroughly reviewed the preclinical and clinical Taxotere data throughout the development process and twice requested outside consultation on the Taxotere NDA from the Oncology Drugs Advisory Committee.*
- c. *The initial and subsequent approvals and the approved labeling for Taxotere were appropriate and based on good science and good regulatory principles.*
- d. *Information on alopecia has been included in Taxotere labeling beginning with the initial approval through the present. Inclusion of "alopecia" in the Adverse Reactions section was and is appropriate as alopecia does not meet the regulatory definition of a serious adverse reaction as provided in 21 C.F.R. 312.32 and in 21 C.F.R. 314.80.*
- e. *From initial approval up to 2010, the Taxotere Patient Package Insert, which undergoes review and approval by FDA, indicated that hair loss associated with the use of Taxotere "generally grows back". This statement was removed by FDA during a 2010 labeling review. The exact reason for FDA's edits is unclear, although FDA made similar changes to the Patient Package Insert for other taxanes in the same time period.*
- f. *In 2004, based on clinical trials data, Sanofi included a statement in draft labeling that proposed listing what it termed "Other persistent reactions", which included alopecia among the several listed with Taxotere chemotherapy regimens. FDA removed this section from the labeling without further comment. In my opinion, Sanofi's inclusion of this statement was appropriate; FDA's reasoning for its removal is unclear and was within its regulatory authority for control of medical product labeling.*
- g. *The 2011 Sanofi document "Clinical Overview Docetaxel – Persistent Alopecia" was methodologically and scientifically appropriate in responding to the request by the French regulatory agency for a review of reports of persistent alopecia.*
- h. *Regulatory and labeling decisions may vary from country to country. In my experience, FDA makes independent regulatory decisions and is not bound to follow decisions made by other, non-U.S. regulatory agencies. For instance, in 2011, both the 10-year TAX 316 data and the Sanofi clinical overview of*

persistent alopecia were submitted to FDA. FDA did not require a labeling change addressing persistent alopecia based on those data.

- i. Plaintiffs' experts' causation opinions are based on case reports and review of FAERS case report data, the weakest forms of scientific evidence. The currently available scientific evidence does not support an unequivocal causal role for Taxotere alone in persistent or permanent alopecia; in my opinion, the data are too confounded to make such an assertion with any scientific or medical certainty.*

III. STATEMENT OF OPINIONS

FDA'S REGULATION OF PRESCRIPTION DRUGS

12. FDA is the federal regulatory agency charged with protecting the public health by assuring that pharmaceutical products, medical devices including devices that use and emit radiation, biological products, veterinary products, tobacco and tobacco products, and foods and cosmetics are safe and that the therapeutic products are effective for their intended uses. To accomplish its public health mission, FDA employs over 10,000 people nationwide. Among FDA's employees are several thousand scientists and other professionals, as well as support staff.

13. There are currently seven Centers within FDA, including the toxicology research center located in Arkansas. CDER, the pharmaceutical product regulatory center, is the largest drug regulatory body in the world. Based on the laws and regulations that FDA enforces and applies, virtually all aspects of the clinical research and development, manufacturing, evaluation, labeling, distribution, promotion, and postmarket safety surveillance of drugs in the United States fall under FDA's regulatory authority.

14. Within CDER, there are several offices and multiple divisions and branches within those offices. There have been numerous reorganizations of CDER over time with changes in regulatory and scientific assignments and new organizational designations. The premarket review offices and divisions within CDER, which are generally organized by

therapeutic classes of drugs, have been reorganized and renamed based on changes in therapeutic class assignments or regulatory procedures. Within the premarket Office of New Drugs are the Offices of Drug Evaluation I through IV, the Office of Antimicrobial Products and the Office of Hematology and Oncology Products. Additional Offices within CDER include the Office of Prescription Drug Promotion, the Office of Epidemiology and Biostatistics, the Office of the Center Director, and the Office of Regulatory Policy, among other scientific and management divisions responsible for the support of pharmaceutical product regulation in the U.S.

15. However the regulatory assignments are distributed, and premarket divisions designated, FDA professionals within review divisions have responsibility for the review and approval of proposed new drug products as well as the continued review, approval, ongoing labeling and postmarket safety review for drugs approved for marketing in the U.S. In my experience, CDER employees are dedicated professionals who are committed to their role in protecting the public health through thorough and ongoing reviews and monitoring of the safety and effectiveness of pharmaceutical products on the U.S. market.

THE DRUG APPROVAL PROCESS

16. Investigational New Drug Application: FDA regulations generally require that a drug manufacturer submit to FDA an Investigational New Drug Application (IND), also known as an investigational new drug exemption request, prior to use of a new, unapproved drug product in a human being in the U.S. The IND or “exemption request” is so called because it is a request of FDA by the company for exemption from the prohibition against introducing or delivering for introduction into interstate commerce a pharmaceutical product that is not in compliance with FDA’s drug approval requirements - in other words, a pharmaceutical product that is an unapproved drug. When a new IND is submitted to FDA, a team of scientists including physicians, chemists, pharmacologists, and toxicologists is assigned to review the data submitted

in the IND. The IND must contain, among other things, extensive information on the manufacture of the drug; animal studies of pharmacology and toxicology, which serve to estimate the potential safety of the drug product for humans; an investigator's brochure serving as labeling for the investigational new drug product; and one or more protocols for the initial studies in humans. The scientific review of the IND by FDA forms the basis for determining whether the drug product is safe enough for testing in humans, based on the data and study protocols included in the IND submission.

17. If an IND is allowed to proceed, the safety information derived from the initial studies, generally conducted in healthy volunteers, is used to determine if further drug development is appropriate. Once some level of safety assurance for human subjects is provided from the early clinical trials, the drug product may be studied in more extensive clinical trials to establish effectiveness while data on safety for the intended population continues to accrue. The IND stage of drug development represents the gateway to further development. FDA can and sometimes does place a hold on further clinical development at the IND stage when the safety of the product for use in humans is in question. The foremost consideration for FDA in clinical drug development is safety for the clinical trial participants and then ultimately for the indicated population.

18. New Drug Application Review: When a sponsor feels that it has collected sufficient information to demonstrate that its new drug product is safe and effective for a particular indication, the company then submits a New Drug Application to FDA. It is important to understand that FDA scientists are actively involved in the design, review and assessment of clinical trials throughout drug product development and prior to submission of the NDA. The FDA has described a range of study designs in its regulations that can serve as "adequate and

well-controlled investigations” upon which claims of effectiveness for a new drug or new indication for an approved drug may be based. These phase III, pivotal trial study designs can provide “substantial evidence” in support of product approval for a specific indication. As noted in 21 C.F.R. § 314.126 (b)(2)(ii), an acceptable pivotal trial design might include two or more dose comparisons of the investigational product plus either a placebo or an active control arm. An active treatment study design is one in which the test drug is compared with a known effective therapy when the condition treated is such that administration of placebo would be contrary to the interests of the patient. (21 C.F.R. § 314.126(b)(2)(iv).) Use of an active control arm in clinical trials is appropriate to avoid negative health consequences for patients if effective drug treatment must be withheld for extended periods of time.

19. Under FDA regulations, an NDA must contain, among other things: (i) reports of all investigations (pre-clinical and clinical) pertinent to the proposed use; (ii) summaries of the safety and efficacy data; (iii) detailed descriptions of the composition of the drug; (iv) description and identification of the methods and facilities used in the manufacture of the drug; (v) product samples (upon request from FDA); and (vi) proposed labeling.

20. The NDA is then rigorously reviewed by FDA scientists and regulatory experts, including supervisory scientists, Office and Division Directors and other officials of FDA, to determine whether the information is sufficient to establish that the drug meets FDA’s safety and efficacy requirements. FDA is well acquainted with a drug when the NDA is submitted because it has followed the drug in the prior IND developmental process. FDA offers significant input on the development process, including comments on and requirements for alterations in clinical trial design. In general, the same team of scientists and physicians who reviewed and followed development of data during the IND process conducts a careful review of the NDA and prepares

detailed reports on their findings. FDA also may convene an Advisory Committee to obtain additional recommendations and opinions on safety and efficacy, particularly when considering approval for a drug product in a novel therapeutic or chemical class. After intensive review by the FDA team and their supervisors, FDA then issues a letter to the sponsor informing them of the Agency's decision on approval. Prior to July 2008, the letter would indicate whether the drug product is approved for marketing, approvable, or not approvable. If the NDA was considered approvable, the letter would indicate what additional submissions were required to permit the product to gain approval for marketing. Since August 11, 2008, FDA has provided the sponsor with either an approval letter or, if FDA determines that it will not approve the application in its current form, a "complete response" letter describing the specific deficiencies that FDA has identified in the application. (21 C.F.R. § 314.110.)

21. All drugs, including prescription drugs, involve risks to patients who use the drugs to benefit their health. When FDA approves an NDA, it means that the scientists and regulatory experts considering approval have reached a decision that the drug has been shown to be safe and effective when used as recommended in the approved labeling. (21 C.F.R. §§ 314.105, 314.125.) In other words, approval for marketing means that the FDA has found that the anticipated benefits of the drug generally outweigh the known risks when used in accordance with the approved labeling. Approval for marketing also recognizes the inherent and practical limitations of studying a drug prior to approval. In the absence of known, class-related adverse events likely associated with a new member of the class, long-term safety studies with adverse events as primary endpoints are not required prior to approval. Such a trial, focused only on detection of undefined potential adverse events, would not be considered an ethical study design. Risk-benefit assessment is an essential part of the drug approval process and involves

judgment on the part of the reviewers. No drug is completely safe, and no drug is expected to be effective in treating every patient. Similarly, the option of offering no treatment for a clinical condition may confer health risks that must also be recognized and appreciated by patients and physicians or other care providers.

PRESCRIPTION DRUG LABELING

22. As required by 21 C.F.R. § 314.50(e)(2)(ii), “Content and Format of an NDA,” a drug sponsor must submit draft labeling for its proposed new drug product as part of the NDA submission. The labeling for a drug is intended to provide the essential information a physician or other prescriber needs to know in order to safely and effectively prescribe the drug for his or her patient. Information in the product labeling is derived from the NDA and from other information available about the specific drug or similar drug products. The final product labeling emerges from discussions between the company and the review team at FDA, based generally on the draft labeling submitted by the company with its NDA. The labeling that is approved with the approval of the drug product is usually the result of extensive discussions between the company and FDA. However, in all instances, FDA makes the final determination on the content and language of the labeling, as well as the placement of information in the labeling, based on its independent review of the supporting data and in accordance with its regulations. (21 C.F.R. §§ 314.125(b)(2)-(8).)

23. General Labeling Requirements: FDA’s labeling requirements for prescription drugs are set out in various regulations including, but not limited to, 21 C.F.R. § 201.56 and 21 C.F.R. § 201.57. The exact format and sequence of information for prescription drug labeling is described in 21 C.F.R. §§ 201.56 and 201.57, with the older version of the labeling requirements now contained at 21 C.F.R. § 201.80.

24. Prior to the 2006 revisions to sections 201.56 and 201.57, the regulations required the Warnings section of the labeling to include information about “serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.” (21 C.F.R. § 201.57(e) (April 1, 2005).) A serious adverse reaction, as used in section 201.57, has been defined as “[a]ny adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.” (21 C.F.R. § 314.80; 21 CFR § 312.32.)

25. Prior to the 2006 revisions, the section of the labeling entitled “Precautions” contained information that did not merit inclusion in the Warnings, including “information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other specific section or subsection of the labeling.” (21 C.F.R. § 201.57(f)(1) (April 1, 2005).)

26. The requirements governing the format of the labeling were revised in 2006. The preambles to the Proposed Rule and Notice of Final Rule published in the Federal Register contain FDA’s comments on the nature and role of prescription medication labeling as well as the labeling process. (65 Fed. Reg. 81082 (Dec. 22, 2000); 71 Fed. Reg. 3922 (Jan. 24, 2006).) These comments shed light on the processes and reasoning FDA employs when drafting and revising labeling. In the preamble to the Final Rule, FDA stated:

The centerpiece of [FDA's] risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. FDA carefully controls the content of labeling for a prescription drug, because such labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use. FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the product's labeling when appropriate.

(71 Fed. Reg. 3934.)

27. As a result of the 2006 revisions, the Warnings and Precautions sections of the labeling were combined. The agency concluded that "observations and suggestions from the physician focus groups..., combined with FDA's experience, have convinced the agency that the distinction between warnings and precautions is perceived by prescribers as being relatively arbitrary and frequently not clinically meaningful." (65 Fed. Reg. 81082 at 81092.)

28. It is my opinion, based on my experience at FDA and my regulatory work since leaving the Agency, that in determining which adverse reactions may be "important medical events" but do not meet the strict regulatory definition of a serious adverse reaction, the Agency considers a variety of factors such as the indication, the relative seriousness of the disease or condition treated, and the incidence of the adverse reaction. (FDA Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products: Content and Format (Oct. 2011), <http://www.fda.gov/downloads/drugs/guidances/ucm075096.pdf>. Accessed 10/22/2018) Thus medical and regulatory judgement are necessary in determining what "important medical events" are of clinical significance and should be included in the "Warnings" or "Warnings and Precautions" section of the labeling. As previously noted, FDA's primary concern during drug

development and postmarket regulation is patient safety, including alerting physicians and patients to important safety and effectiveness information.

29. Approved product labeling is reviewed by FDA and the sponsor on an ongoing basis after drug approval for possible revisions based on new postmarket safety data, changes in the regulatory or scientific knowledge bases, or new information obtained either by the company or by FDA from other sources. Although “a causal relationship need not have been definitively established,” the Warnings and Precautions section of labeling “must be” revised to include a warning about a “clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug.” (21 C.F.R. § 201.57(c)(6)(i).) In this context, reasonable evidence of a causal association means a signal is confirmed and is not merely a “weak” or “potential” signal referred for further evaluation. FDA can and does regularly request postmarket revisions to the labeling, and, under section 505(o)(4) of the FD&C Act, FDA has authority to require safety labeling changes if the agency becomes aware of “new safety information” that it believes should be included in the labeling of a drug. In determining when and where new safety information should appear in the labeling, FDA employs its scientific and regulatory judgment. As the Agency has noted, “interpreting postmarketing safety data is complex, involving analysis of post-approval clinical data and detailed review of a wide range of potentially relevant information, including adverse drug experience reports, pertinent controlled clinical trials and epidemiologic studies, active surveillance efforts, estimates of drug usage and adverse drug experience reporting rates, estimates of background rates of the adverse event, and other relevant information. Decisions about how to address a safety concern often are a matter of judgment, about which reasonable and adequately informed persons with relevant expertise may disagree.” (Draft FDA Guidance: FDA’s Communication to the Public (Mar. 2012))

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm295217.pdf>. Accessed 10/22/2018)

30. Each time the FDA approves a labeling change, the agency reaffirms that the drug is safe and effective when used in accordance with the labeling. Again, FDA scientists and regulatory experts make the final determination of the appearance, location and language of any labeling changes. While acknowledging that pharmaceutical manufacturers have an obligation to assure that their drugs' labeling is not false or misleading, FDA may determine that certain information should be included in the product labeling. "[I]t is irrelevant whether FDA makes that determination before or after approval. . . If the agency were not permitted to revise required labeling based on the product's market experience, its ability to protect the public health would be seriously undermined." (63 Fed. Reg. 66378 at 66383 (Dec. 1, 1998).)

31. Non-indicated Uses: As it has acknowledged repeatedly, FDA is aware of off-label use, and has recognized that in certain contexts, off-label uses may constitute a standard of care. FDA does not generally regulate off-label use since off-label use reflects the practice of medicine, which FDA does not regulate. As a general proposition and in the absence of information suggesting a drug commonly prescribed for an off-label use is associated with a clinically significant risk or hazard to patients, manufacturers cannot amend labeling to add information about findings in non-indicated (off-label) populations. If FDA has information indicating that a particular off-label use poses a significant risk to patients and there is information indicating that the particular off-label use is ineffective, the agency can require that the manufacturer include a statement in the labeling specifically citing the additional risk, lack of efficacy, or unfavorable benefit/risk expectation when the product is used off-label. (21 C.F.R. §§ 201.57(c), (e) (Apr. 1, 2005); 21 C.F.R. 201.57 §§ (c)(2)(ii), (c)(6)(i) (Apr. 1, 2016).)

32. Changes Being Effected: As a general matter, sponsors cannot implement post-approval changes to approved product labeling without prior FDA approval. One limited exception to this rule is known as a Changes Being Effected (“CBE”) Supplement. (21 C.F.R. § 314.70(3)(c) (2006) and subsequent changes.) The governing regulations state that FDA may designate a category of changes in which the holder of an approved application may begin distribution of the subject drug product with new labeling immediately upon the Agency’s receipt of a CBE sNDA (CBE-0). The CBE-0 type changes permitted under this regulation include:

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

- (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;
- (B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdose;
- (C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;
- (D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or
- (E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(21 C.F.R. § 314.70 (c)(6)(iii) (2006).)

33. A so-called CBE-0 supplement may be used by a manufacturer to add to the labeling “newly acquired” safety information. As noted above, the proposed labeling change

submitted to FDA as a CBE-0 sNDA may be implemented upon FDA's receipt of the CBE-0 sNDA. (21 C.F.R. § 314.70(c)(6); 73 Fed. Reg. 2848 at 2849 (Jan. 16, 2008).) The CBE-0 labeling change may be used only to implement labeling changes to Contraindications, Warnings and Precautions, or Adverse Reactions when there is "reasonable evidence of a causal association" between exposure to the drug product and onset of the adverse clinical event. (21 C.F.R. § 314.70 (c)(6)(iii)(A) and 21 C.F.R. § 201.57(c)(6)(i).) The sponsor also must revise all advertising and promotional materials to make them consistent with the newly implemented labeling changes.

34. FDA revised the CBE regulations in 2008 "to reaffirm its longstanding position that a supplemental application submitted under [21 C.F.R. § 314.70] is appropriate to amend the labeling for an approved product only to reflect newly acquired information, as well as to clarify that such a supplemental application may be used to add or strengthen a contraindication, warning, precaution or adverse reaction only if there is sufficient evidence of a causal association with the drug, biologic, or device." (73 Fed Reg. 2848; 73 Fed Reg. 49603 at 49604 (Aug. 22, 2008).)

35. FDA has several options in response to a CBE submission. For instance, FDA may notify the manufacturer that the proposed sNDA requires prior approval before implementation or may deny approval of the language, placement, or inclusion of the proposed changes submitted as a CBE. (21 C.F.R. §§ 314.7(b), (c)(7).) If the manufacturer has already instituted the labeling changes and shipped its product with the new labeling and FDA determines that use of the CBE mechanism or the specific language or placement of the new information is not appropriate, the manufacturer may be subject to regulatory action based on a possible assessment of misbranding. Thus, whether to authorize a change remains "squarely and

solely FDA's" decision. (71 Fed. Reg. 3922 at 3934.) In practice, therefore, manufacturers typically consult with FDA before making any labeling changes. (73 Fed. Reg. 2848 at 2849; 71 Fed. Reg. 3922 at 3934.)

36. Patient Directed Labeling: The professional package insert, or labeling, is intended for the prescriber and other health professionals and is not written for or intended to be used by consumers. Since 1968, FDA may require, or a manufacturer may request, development of patient-directed labeling, written in non-technical language, to be included in the package insert or as separate labeling provided to the patient at the time the product is dispensed by a pharmacist. The intent of this patient information is to alert patients to appropriate use of and adverse reactions associated with the drug product or to provide other important information about the use of the drug such as its contraindications, precautions, and effectiveness. (60 Fed. Reg. 44184 (Aug. 24, 1995).) Regulations located at 21 C.F.R. § 208.1 specifically provide that FDA may require a medication guide where it determines that the nature of the risks and benefits is such that patient labeling is necessary for the safe and effective use of the prescribed product.

FDA AMENDMENTS ACT (FDAAA)

37. As part of the FDA Amendments Act of 2007 (FDAAA), additional authorities were granted to FDA. These authorities, which are discussed in detail throughout this report, include the ability to mandate labeling changes for new safety information, the ability to require REMS, and the ability to institute Post Marketing Requirements (PRMs), including randomized clinical trials and observational studies. From the effective date of FDAAA forward, FDA has unquestionable authority to mandate labeling changes based on new safety information.

FDA ADVISORY COMMITTEES

38. FDA can and does convene panels of outside experts when seeking advice on product approval, labeling, safety, risk/benefit assessments and other scientific and regulatory

matters. (21 C.F.R. § 14.1 *et seq.*) Advisory committee members are generally physicians, statisticians, epidemiologists, and other scientists, as well as consumer and industry representatives. These advisory committee members are experts in their fields and provide FDA with advice on a wide variety of questions and concerns. Like the review divisions in CDER's Office of New Drugs, CDER's advisory committees generally are organized by drug type or disease area so that each panel is populated by scientists who have particular expertise in the drug products addressed by that committee; in addition, there are advisory committees such as the risk management committee that address particular regulatory issues independent of any specific review division.

39. Most advisory committee meetings are open and public. Background, data and analyses from a sponsor and from FDA are provided to committee members prior to the meeting and may be made available to interested parties on FDA's website. Discussion among committee members, question and answer sessions between the committee members and presenters from industry and FDA, as well as comments or testimony by members of the public, are essential parts of the advisory committee process. The committee considers all available information in its deliberations and when making recommendations to the FDA. While FDA carefully considers the recommendations and deliberations of advisory committees, these recommendations and considerations are not binding on the Agency.

REGULATION OF MARKETED DRUGS

40. The FDA has authority over advertising and promotion of prescription pharmaceutical products. Regulations addressing advertisements for approved prescription pharmaceuticals are in 21 C.F.R. § 202.1. In general, promotional materials and advertising pieces that include the brand name of the product and any explicit or implied claims must be consistent with the currently approved labeling and must show fair balance in the presentation of

benefits and risks. Generally, FDA approval of the material is not required prior to publication or use of an advertisement issued after initial marketing approval. (21 C.F.R. § 202.1(j)(1).) Product-specific (branded) advertisements generally must be submitted to FDA “at the time of initial publication.” (21 C.F.R. § 314.81(b)(3)(i).) This is true for every iteration or change in a proposed marketing piece, irrespective of the media through which it will appear or the audience to which it is directed. Pharmaceutical product sponsors may voluntarily seek pre-publication or pre-use review of advertisements at any time during marketing or may be directed by FDA to submit such materials for review prior to use. (21 C.F.R. § 202.1(j)(4).) The main organizational unit within FDA that reviews advertising for prescription medications is the Office of Prescription Drug Promotion (OPDP), formerly known as the Division of Drug Marketing Advertising and Communications (DDMAC) in CDER. OPDP has several review teams that focus on specific therapeutic classes of products and specific types of advertising. The professional review groups evaluate materials intended for prescribers and other health care professionals

41. OPDP states that its mission is:

To protect the public health by ensuring that prescription drug information is truthful, balanced, and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement and education program, and by fostering better communication of labeling and promotional information to both healthcare professionals and consumers.

(FDA: Office of Prescription Drug Promotion,

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm>. Accessed 10/15/2018).

42. In addition to its review of submitted ads, FDA conducts its own monitoring of promotional activities, including by attendance at professional meetings and events. OPDP also

may become aware of potentially violative advertising or promotional activities from competing manufacturers; from consumer groups, physicians, pharmacists; or from other sources who complain to the Agency. In fact, FDA has created a program called “Bad Ad” to encourage prescribers to alert the Agency to potentially violative advertising and promotional activities of which they become aware. (FDA: Truthful Prescription Drug Advertising and Promotion, Bad Ad,

<https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/drugmarketin gadvertisingandcommunications/ucm209384.htm>. Accessed 12/20/2018).

43. If OPDP determines that an advertisement—whether branded or unbranded—is not in compliance with the regulations, it has several options, including written correspondence (“untitled” and “warning” letters), injunctions and consent decrees, referrals for criminal investigation and prosecution, and seizures of violative materials. Untitled letters are used for less serious violations, such as overstating the effectiveness of a drug, while Warning Letters are used for serious situations including repeated violations or violations that may affect a significant health and safety risk. Untitled letters and Warning Letters are reviewed by the FDA Office of the Chief Counsel before issuance and are intended to serve as a precursor to further enforcement action if the violation is not remedied. If the violation continues, civil or criminal actions may be initiated based upon the nature and circumstances surrounding the violation. (Statement of Janet Woodcock, M.D., Director for Center for Drug Evaluation and Research, FDA, before the Senate Special Committee on Aging, 108th Cong. (Jul. 22, 2003) (<https://wayback.archive-it.org/7993/20170112233711/http://www.fda.gov/NewsEvents/Testimony/ucm115080.htm>).

44. Warning letters and untitled letters addressing advertising and promotional materials or other inspection and compliance activities are published and publicly available on

the FDA website. (FDA: Inspections, Compliance, Enforcement, & Criminal Investigations, www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm.) Such letters may serve to alert manufacturers of FDA's current concerns in relation to advertising and promotion. The language used in these letters (false, misleading, misbranded) reflects the regulatory language of 21 C.F.R. §200, 201 and 202, that allows CDER to comment upon and initiate regulatory actions based on review of advertising, labeling or marketing materials. In the past, DDMAC (now OPDP) publicly indicated that among its priorities in reviewing and monitoring advertising and promotion are materials concerning newly approved products or products with new indications; DTC TV and radio advertisements; promotional materials about which FDA has received complaints from competitors, healthcare providers or consumers; and promotional materials concerning products and companies that have been the recent focus of compliance actions. Thus, manufacturers may find guidance regarding FDA's monitoring practices and priorities based on the content of untitled or warning letters to other manufacturers of similar pharmaceutical products and may proactively review or revise their own materials based on recent compliance actions published on the FDA website.

45. Off Label Use of Marketed Pharmaceutical Products: "Off-label" use of marketed pharmaceutical products generally means that the product is used in treating a patient population, condition, or disease not described in the current "Indications and Usage" or using a dose or dosing interval not provided for in the "Dosage and Administration" section of the approved product labeling. Off-label prescribing is a very common practice in the U.S., especially among pediatric physicians. Approved medications frequently are used for indications or in populations which are not included in the product labeling.

46. FDA has long maintained that off-label use of an approved pharmaceutical product is a matter of the practice of medicine and that FDA does not regulate the practice of medicine. As such, the decision about prescribing a particular product for an individual patient rests with the prescribing physician and the patient, whether or not the patient's health condition is addressed by the product label.

47. While FDA does not have authority over a physician's or a patient's off-label use of an approved product, it does regulate the product sponsor's advertising, promotion and marketing of approved products and views promotion of off-label uses of pharmaceutical products as inconsistent with its regulations. However, there are circumstances in which such information may be provided to a physician, along with the currently approved product labeling.

48. Distribution of Scientific Articles: Manufacturers may disseminate medical and scientific information on unapproved uses of drugs and medical devices, so long as the publication and its dissemination meet certain criteria, including that the publication is peer-reviewed, is in the form of a complete and unabridged document, is neither false nor misleading, that the proposed off-label use does not pose a significant risk to the public health, and the article or publication is accompanied by the full, approved labeling for the drug or medical device, and provides certain disclaimers. "FDA recognizes that the public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical products." (FDA Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (Jan. 2009); *Washington Legal Foundation v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999).)

POSTMARKET SAFETY SURVEILLANCE

49. Under 21 C.F.R. § 314.80, the FDA has established a systematic approach to postmarket safety surveillance using, among other data sources, reports of adverse events associated with the use of approved drugs marketed in U.S, whether the events occurred domestically or during the course of foreign marketing of the product. The regulations addressing postmarket safety surveillance, which were promulgated in 1985 and have been updated since then, are based on federal law and sound scientific principles.

50. Basically, postmarket safety surveillance provides information to FDA and to the sponsoring company about the safety profile of an approved product following its market introduction. It is an accepted fact that neither the full safety nor effectiveness profile of a pharmaceutical product can be known at the time of product approval. (Draft FDA Guidance: FDA's Communication to the Public (Mar. 2012) available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm295217.pdf>.) Generally, preapproval clinical trials are in a relatively small number of patients for a relatively short duration. Often the population is a well-defined patient population with few comorbidities and few concomitant medications. Once a drug enters the marketplace, physicians are free to prescribe it to patients for indications and at doses which they believe appropriate for their patients. Following market introduction, information about real-world use in a larger and more diverse group of patients and for longer time periods than in the initial clinical trials becomes available. Thus, with a wider population exposure, it is not unexpected that a newly approved pharmaceutical product may be found to be associated with potential new adverse events, drug interactions, and uses not seen in the pre-approval trials.

51. FDA regulations anticipate the need to continually review and assess the safety profile of marketed drugs. Under 21 C.F.R § 314.80(b), FDA requires that companies review

spontaneously reported adverse events received by the company from all sources. These sources may include reports submitted by physicians and other healthcare providers, by patients, or by other individuals or other manufacturers. Both the manufacturer and FDA review the published medical literature, unpublished clinical data, postmarket clinical trials, and adverse events reports from use of the product both within and outside of the U.S. to determine if new safety information about a drug may be emerging. Companies are required to submit quarterly safety update reports for the first three years after marketing and annually thereafter to provide FDA with their assessment and analysis of the available safety data from all sources. (21 C.F.R. § 314.80(c)(ii).) Adverse event reports submitted to the FDA are generally evaluated by two groups within the Agency. One group responsible for the review, coding and processing of such reports, formerly known as the Office of Epidemiology and Biostatistics, includes physicians, epidemiologists, pharmacists and other scientists. The other group monitoring postmarket safety reports is the review team responsible for approval and labeling of the drug. Adverse Events (AEs) are evaluated and may be independently coded by FDA and entered into a computerized, automated database. Review of AEs associated with the use of specific drug products or product classes can be conducted using AE data alone or in combination with information from other sources.

52. Under 21 C.F.R. § 314.80(c), the FDA has established a triage system for reviewing adverse event reports. Serious, unlabeled events received from any source must be reported to the FDA by the manufacturer within 15 days from “initial receipt” of the information by the applicant. Serious labeled reactions do not routinely fall under the 15-day reporting requirement. Other reporting requirements include submission of periodic reports (either annually or quarterly), listing those reports identified in 21 C.F.R. § 314.80(c)(2) and submission

of annual reports covering information specified in 21 C.F.R. § 314.81(b)(2). Upon request, FDA may agree to permit manufacturers to submit Periodic Safety Update Reports (PSURs) required under the European Union postmarket reporting scheme in lieu of the annual Periodic Adverse Drug Event Reports.

53. The purpose of the adverse event review engaged in by FDA is to determine if any new safety signals (i.e., new information suggesting an association between an event and a drug) may be emerging in the postmarketing experience. “[*S*]afety signal refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product’s use. . . . Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event.” (FDA Guidance: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment at 4 (Mar. 2005) <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf>.) Signal detection may occur in a number of ways. Periodically, FDA will analyze its entire adverse event and medication error database (FAERS) looking for rare and unexpected events or any events occurring at unexpected rates. This kind of statistical analysis is done by FDA not for a specific drug or class of drugs, but across the entire universe of approved products. A second form of signal detection may result from a reviewer’s or reporter’s observation of even a small number of unusual, rare or essentially unique events, typically for a specific drug or class of drugs. A signal also may be detected from review of the medical or scientific literature, including clinical trials or observational epidemiological data.

54. It should be emphasized that while FDA uses adverse events for signal generation, it does not use them to assess causation. This is consistent with good pharmacovigilance practices and how epidemiologists—both inside FDA and throughout the

scientific community—approach the hierarchy of evidence. Case reports like those submitted as adverse event or adverse experience reports are generally considered the lowest form of scientific evidence. While they are useful for hypothesis generating, they often lack or incorrectly convey important clinical information, are subject to reporting and attribution biases, and otherwise are too unreliable for the purposes of determining cause and effect relationships.

55. Among the well-recognized limitations of reported adverse events is that they are often confounded by reporting and attribution biases. For example, identifying, attributing and reporting potential adverse drug events may be influenced by how recently a drug has been introduced to the market, how long a patient has been on a drug, the presence of publicity concerning the product or a specific event (including from litigation), the seriousness of the event, and characteristics of the patient population such as age, pregnancy, or co-morbid conditions.

56. The greatest utility of case reports in the regulatory postmarket setting, as in epidemiology generally, is to bring to the attention of a manufacturer or regulatory agency a potential new problem that may be associated with the use of a marketed medical product. Generally, case reports alone cannot be used to establish a causal relationship between a product and an outcome nor can postmarket adverse event reports be used in determining a rate of occurrence in the exposed population. Case reports submitted to FDA or a manufacturer as adverse event reports may be used to generate a postmarket safety signal requiring further assessment and evaluation based on the hypothesis that there may be a causal association. In developing an hypothesis to test in outside data sources, a case definition must be developed based on the available case-related information. A case definition is often critical to a rigorous assessment of safety signals because it allows reviewers to have a pre-determined and thus less

biased means of deciding whether what they are seeing reported aligns with the potential risk signal they are looking for. Further evaluation and risk assessment may be accomplished through pharmacoepidemiologic studies, registries or surveys, or in some cases, from double-blind, randomized controlled clinical trials, depending on the nature of the event, the suspect drug, and the population in which the drug is used. However, as the FDA has noted, “Clinical trials are impractical in almost all cases when the event rates of concern are less common than 1:2000 to 3000.” (FDA Guidance: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment at 13 (Mar. 2005)

(<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf>).

57. In general, appropriately analyzed data from prospectively designed clinical studies (specifically randomized, double-blind, multi-center, controlled clinical trials) are considered the most reliable source of information on estimating the safety and effectiveness of any medical product or intervention. Next in order of scientific validity would be data from other types of prospectively designed clinical trials, then data from observational studies, from case series, and, finally, from individual case reports, which are the least reliable and, as mentioned, absent rare circumstances, not useful in assessing causality.

58. It is my opinion that the FDA’s regulations and requirements for reporting and review of adverse events, signal monitoring and detection, including assessment of observational and clinical trial data, are based on good science and sound judgment accepted generally in the scientific community.

FDA's REGULATION OF DOCETAXEL (Taxotere®)Initial Approval

59. The IND for Taxotere® was submitted to FDA's Division of Oncology Drug Products October 2, 1990. The New Drug Application was submitted July 27, 1994. Initial indications were for metastatic breast cancer patients in whom previous chemotherapy, including an anthracycline (unless otherwise contra-indicated), had failed. Taxotere was granted accelerated approval review status and taken to ODAC for consideration on December 13, 1994. Initially, ODAC did not recommend approval of Taxotere, in part due to the apparent increased rate of febrile neutropenia among breast cancer patients assigned to the docetaxel arm as compared to paclitaxel (Taxol®) -exposed patients. The ODAC panel raised additional issues including concerns about performance status, fluid retention and sepsis-related deaths in docetaxel-exposed patients. ODAC's concerns did not involve alopecia.

60. Following denial of the marketing application for Taxotere by ODAC, FDA and RPR entered into discussion about the ODAC meeting. RPR clarified that the difference in rates of febrile neutropenia among docetaxel versus paclitaxel patients was due to a broader definition of "febrile neutropenia" in the docetaxel clinical trials than had been used in the paclitaxel NDA. The company provided additional data for septic deaths and fluid retention, which satisfied FDA's questions the toxicity profile. (Sanofi_00399197, Sanofi_001687).

61. The Taxotere NDA went back to ODAC October 17, 1995 and the committee recommended approval for metastatic, treatment-failure breast cancer. Dexamethasone pre-treatment was recommended to reduce the risk for fluid retention.

62. FDA subsequently found the Taxotere NDA approvable on October 27, 1995. (Sanofi_00502775). The Taxotere NDA was originally approved on May 14, 1996, for the

treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy. (Sanofi_01380011). The Taxotere NDA was reviewed and approved under FDA's accelerated approval provision. (Sanofi_01380011). These provisions are for drug products that treat serious or life-threatening illnesses and that provide patients with meaningful therapeutic benefit as compared to existing treatments. (21 C.F.R. 314.500, 21 C.F.R. 314.510).

63. Prior to approval, FDA thoroughly reviewed the safety profile for Taxotere, including the risk of alopecia. (Sanofi_00654998). The risk of alopecia was also presented at both the 1994 and 1995 ODAC meetings. (Sanofi_001317, Sanofi_001445, Sanofi_001687)).

Adequacy of the Taxotere Label

64. It is my understanding that Plaintiffs in this litigation allege that Taxotere caused them to develop permanent alopecia and that the Taxotere labeling is inadequate because it does not contain a warning about permanent alopecia. It is my opinion that Taxotere has always been appropriately labeled during its marketing history in the United States. The FDA-approved Taxotere label has always warned of alopecia in both the physician- and patient-package inserts.

65. The initial FDA-approved Taxotere label included hair loss in physician- and patient package inserts. The initial label included a patient package insert that stated:

Loss of hair occurs in most patients taking Taxotere (including the hair on your head, underarm hair, pubic hair, eyebrows and eyelashes.) Hair loss will begin after the first few treatments and varies from patient to patient. Once you have completed all of your treatments, hair generally grows back.

(Sanofi_000003). The language in the patient package insert concerning "Hair Loss" was the same from the time of initial approval until 2010 when FDA made changes to that section of the patient information leaflet.

66. The initial FDA-approved physician United States Package Insert (“USPI”) provided rates of “alopecia” in Taxotere treatment. Alopecia occurred in 80% of patients and was severe in 61.8% of patients.

67. Information concerning alopecia associated with Taxotere was in the “Adverse Reactions” section of the physician USPI and was provided in the patient package insert or patient information leaflet in a section entitled “*What are the possible side effects of Taxotere?*”. The “Adverse Reactions” section of the physician-directed labeling is and was the appropriate place to include the term alopecia. Alopecia is an adverse reaction as defined in 21 C.F.R. § 201.57(c)(7). According to the labeling regulations, an adverse reaction is an “undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.” Alopecia is neither unexpected in the course of treatment with a cancer chemotherapeutic agent nor does it meet the regulatory definition of a serious adverse event. It would have been inappropriate to include “alopecia” in the “Warnings” or “Warnings and Precautions” section of the USPI.

68. The Taxotere USPI has at all times appropriately provided physicians and prescribers with information on the risk of alopecia associated with its use. The clinical definition of alopecia is simply “hair loss.” It does not mean, as Plaintiffs have repeatedly suggested, “temporary hair loss.” Alopecia is a term that encompasses all forms of hair loss, temporary or permanent, widespread or patchy. There is no consensus definition by regulation for “ongoing,” “persistent,” “permanent,” or “irreversible” alopecia. While the Medical Dictionary for Regulatory Activities (MedDRA), the dictionary FDA uses and requires companies to use to code adverse events, contains an entry for the term “alopecias,” it does not contain entries for “ongoing,” “persistent,” “permanent,” or “irreversible” alopecia. For these

reasons, it is my opinion that the term “alopecia” appropriately characterized the hair loss associated with docetaxel use.

69. On March 17, 2004, Sanofi submitted sNDA S-029 seeking an indication for Taxotere use in combination with doxorubicin and cyclophosphamide for patients with operable node-positive breast cancer. (Sanofi_00427233). With this submission, Sanofi proposed revisions to the Taxotere USPI relating to the new proposed indication and other information from the TAX 316 study. With respect to alopecia, Sanofi proposed updating the Adverse Reaction section of the USPI to add a subsection:

Other persistent reactions

The following events were observed to be ongoing in the TAC-treated patients at the median follow-up time of 55 months: alopecia (22/687), amenorrhea (133/233), neurosensory (9/73) and peripheral edema (18/112). These events were also observed in the FAC arm during the follow-up period: alopecia (9/642), amenorrhea (101/186), neurosensory (2/15) and peripheral edema (3/19).

(Sanofi_01296737). In addition to the original submission in March, Sanofi resubmitted this labeling proposal to FDA in June and August 2004. (Sanofi_00355202; Sanofi_00354861; Sanofi_04817146).

70. FDA had multiple internal meetings to discuss the Taxotere labeling for the adjuvant breast indication. (Sanofi_04817147). After a series of labeling discussions between Sanofi and FDA, FDA deleted Sanofi’s proposal to add the “**Other persistent reactions**” subsection to the USPI. Based on available documents, it is clear that Ann Staten at FDA deleted the “**Other persistent reactions**” subsection in edits made on August 10, 2004. (Sanofi_04539472). There was no reason provided for the deletion. The revised label reflecting FDA’s revisions was sent to Sanofi on August 11, 2004. (Sanofi_04817139). FDA approved

NDA supplement s-029 on August 18, 2004 without the “**Other persistent reactions**” information Sanofi proposed. (Sanofi_04539390).

71. Additional indications for Taxotere were approved after appropriate data development by Sanofi and thorough review by FDA. In 1998, Taxotere was approved for treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy. In 1999, Taxotere was approved for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. In 2002, Taxotere was approved for use in combination with cisplatin for the treatment of unresectable, locally advanced or metastatic non-small cell lung cancer in patients who had not previously received chemotherapy for that condition. In May 2004, Taxotere was approved for use in combination with prednisone for the treatment of patients with androgen independent (hormone-refractory) metastatic prostate cancer. In August 2004, Taxotere was approved for use in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable, node-positive breast cancer. In March 2006, Taxotere was approved in combination with cisplatin and fluorouracil for the treatment of advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not previously received chemotherapy for advanced disease. In October 2006, Taxotere was approved for use in combination with cisplatin and fluorouracil in the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck. With each approval, FDA reviews the entire label and there is an opportunity for FDA to require changes to any part of the label.

72. As discussed earlier, the language in the patient-package insert concerning “Hair Loss” was the same from the time of initial approval until May 2010 when FDA made what appear to be class-wide changes to that section of the patient information leaflet. As part of its

review of Sanofi's sNDA S-059 to update the Pediatric Use and Human Pharmacokinetics sections of the Taxotere labeling, FDA modified the Taxotere patient labeling. During that labeling review and modification, FDA rewrote the patient information section, including the discussion of hair loss. FDA proposed to include a single bullet point listing hair loss as one of the most common side effects of Taxotere and to add advice to the patient to "Tell your doctor if you have any side effect that bothers you or does not go away." FDA also proposed to include a listing of the common adverse reactions from Taxotere, including hair loss, at the beginning of the Adverse Reactions section of the labeling.

73. A similar change was made to the Taxol label in August 2010, indicating what appears to be class-type labeling changes for the taxane labels. In 2000, the Taxol patient labeling included a similar description of hair loss as the 2000 Taxotere patient labeling. In August 2010, the Taxol patient labeling was changed to address hair loss as a single bullet point as one of the most common side effects of Taxol, mirroring the FDA-initiated change to the Taxotere patient labeling approved in May 2010. (Taxol, NDA 20-262, approved August 13, 2010).

74. Abraxane, another taxane in the same class as Taxotere, went through a similar label change. When Abraxane was first approved in 2005, the Patient Information noted in the "Hair Loss" section that: "*Hair generally grows back after you've finished your ABRAXANE treatment.*" (Abraxane, NDA 21-660, approved January 7, 2005). The Abraxane labeling approved June 26, 2009 contained that same language. (Abraxane, NDA 21-660/s-022). By 2011, the Abraxane patient labeling was changed to address hair loss as a single bullet point as one of the most common side effects of Abraxane, just as in the FDA-initiated change to the

Taxotere patient labeling and the change in the Taxol labeling in August 2010. (Abraxane, NDA 21-660/s-025).

75. Given these class-wide changes, it was reasonable for Sanofi to accept FDA's proposed changes to the Taxotere patient labeling, including the changes involving the bulleted mention of hair loss.

76. On March 23, 2015, FDA requested that Sanofi provide, by April 10, 2015, a summary of cases of persistent total or partial alopecia associated with docetaxel use. (Sanofi_01574962). Sanofi submitted a timely Response to Agency Request on April 10, 2015. The content of the response is discussed in more detail below.

77. On October 2, 2015, FDA requested that Sanofi "Provide any additional information regarding permanent or irreversible alopecia," and "Amend the package insert in Section 6.2 (Postmarketing Experience) (and patient information, if appropriate) to add information on permanent or irreversible alopecia," within 60 days. (Sanofi_00805353).

78. On November 24, 2015, Sanofi provided a response to FDA, which included an updated clinical overview evaluating docetaxel and permanent alopecia. Sanofi also provided a CBE labeling supplement to update the Postmarketing Experiences in the Adverse Reactions section of the Taxotere labeling and an update to the patient information. Sanofi proposed adding to the USPI "Cases of permanent alopecia have been reported" under "Cutaneous" in Postmarketing Experiences in the USPI.

79. Sanofi also proposed adding in the Patient Information a bullet point under "The most common side effects of TAXOTERE include: "hair loss: in most cases normal hair growth should return. In some cases (frequency not known) permanent hair loss has been observed." (Sanofi_03333249).

80. FDA’s Medical Reviewer agreed with Sanofi’s labeling proposal. (NDA 20-449, s-075, Medical Review, Prowell, T., December 7, 2015). FDA’s clinical reviewer stated: “While alopecia occurs in virtually all patients who receive docetaxel, there have only been 2,172 reports to the Sponsor of alopecia, and therefore the true incidence of permanent alopecia is unknown and cannot be reliably estimated given the limitations of the available data. The Sponsor and FDA concur that the available evidence supports a potential causal association between docetaxel and permanent alopecia and that the label should be updated to alert clinicians and patients of this possibility.” (NDA 20-449, s-075, Medical Review, Prowell, T., December 7, 2015).

81. On April 11, 2018, Sanofi submitted a Supplemental New Drug Application providing for the addition of certain safety-related information to the Taxotere USPI. Specifically, Sanofi proposed the addition of “Enterocolitis and Neutropenic Colitis” to Section 5 “Warnings and Precautions” as well as updates to “Hypersensitivity Reactions” in that same section. The sNDA also proposed updating Sections 6 “Adverse Reactions”, 6.2 “Postmarketing Experience”, and 17 “Patient Counseling” to reflect the changes made to Section 5. Some of these labeling changes are intended to distinguish between the risk of adverse events observed over the course of the 8-year median follow-up for TAX 316 and adverse events that were persistent following completion of the trial. The persistent adverse events included peripheral neuropathy, alopecia, amenorrhea, peripheral edema, lymphedema, asthenia, and myelodysplastic syndrome/acute myeloid leukemia. (NDA 20-449/s-079, FDA Approval Letter, October 5, 2018).

82. With respect to alopecia, Sanofi proposed, and FDA approved, the addition of the following language in Section 6.1 “Clinical Trials Experience” of the Taxotere USPI:

Skin and subcutaneous tissue disorders

In study TAX316, alopecia persisting into the follow-up period after the end of chemotherapy was reported in 687 of 744 TAC patients (92.3%) and 645 of 736 FAC patients (87.6%). At the end of the follow-up period (actual median follow-up time of 8 years), alopecia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%).

83. This is an appropriate labeling update with respect to alopecia. At all times, the FDA-approved Taxotere label has been reasonable, adequate, and truthful.

84. On September 24, 2010, Sanofi submitted to FDA the final clinical study report for TAX 316, containing 10-year follow-up data. (Sanofi_01288423). That final study report contained the same data on alopecia that was eventually added to the Taxotere USPI in 2018. (Sanofi_0264952). At the time Sanofi submitted the final clinical study report, Sanofi did not propose a labeling change because the safety and efficacy data from the TAX 316 final analysis were consistent with the known profile of docetaxel and the TAC regimen. (Sanofi_02649521, Gustavson Dep. at 247 (“I think that the reason that the labeling change was not warranted is it was not deemed to – needed to be helpful as prescribing information.”)). Given the consistency of the TAX 316 data, I agree that it was reasonable and appropriate for FDA and Sanofi not to update the alopecia information in the Taxotere USPI, especially since FDA had struck a similar proposed label change in 2004.

85. FDA reviewed the TAX 316 final clinical data and on September 23, 2011, concluded that Sanofi had fulfilled its postmarketing commitment with respect to the TAX 316 study. FDA could have, but did not, request or require a label change based on the updated TAX 316 data. (Sanofi_00262024).

Taxotere European Label

86. Plaintiffs in this litigation claim that the Taxotere USPI was somehow inadequate because it did not contain the same information on alopecia as the Taxotere European label, also known as the Summary of Product Characteristics (SmPC). This claim ignores the fact that it is not unusual for regulatory and labeling decisions to vary from country to country. In my experience, FDA makes independent regulatory decisions and is not bound to follow decisions made by other, non-U.S. regulatory agencies.

87. For example, while FDA rejected the language Sanofi proposed adding to the Taxotere USPI in 2004 about “Other persistent reactions,” the European Medicines Agency (EMA) approved the same language and it was therefore added to the SmPC.

88. In addition, both the 10-year TAX 316 data and the Sanofi 2011 clinical overview of persistent alopecia were submitted to FDA and EMA. While FDA did not request or require a labeling change addressing persistent alopecia based on those data, EMA requested that additional information about the possible irreversibility of alopecia be added to the SmPC. (Sanofi_01094525). It was the EMA’s request that led to the addition of the language “Cases of persisting alopecia have been reported” to the SmPC in 2011. (Sanofi_05413055).

89. For these reasons, I disagree with any claim that the Taxotere USPI was inadequate because it did not contain identical language to the SmPC.

DDMAC LETTERS

89. I have reviewed the enforcement letters from FDA’s DDMAC (now OPDP) that Sanofi received relating to its promotion of Taxotere. None of those letters involved the promotion of Taxotere for the adjuvant treatment of breast cancer. In addition, none of the

letters involved the discussion of the risk of alopecia or persistent or permanent alopecia from Taxotere use.

ALOPECIA MONITORING AND REPORTING

90. As discussed in more detail above, good pharmacovigilance practices are described in FDA regulations and an FDA Guidance. One component of postmarketing safety surveillance is the collection, maintenance, reporting, and evaluation of spontaneous postmarketing adverse event data. Although it is important to collect and analyze these data, as such reports may provide a signal indicating areas for further investigation, adverse event reports cannot be used to determine causality.

91. Based on my review of the materials in this case, Sanofi met or exceeded its regulatory obligations in its Taxotere periodic reporting to FDA. Periodic reports were submitted in a timely fashion. Those reports summarized all necessary adverse event reports, included extensive information about serious adverse events when possible, and contained periodic analyses of specific adverse events. Sanofi also submitted expedited reports as required for all cases of serious and unexpected adverse events, both foreign and domestic.

92. It is important to note that postmarketing reports of alopecia do not meet the criteria for expedited reporting, as alopecia is neither a serious adverse event (as defined in the regulations), nor is it unexpected. As previously noted, information on alopecia has always been in the FDA-approved USPI for Taxotere, including in the patient information materials, which are approved by FDA.

93. With respect to its reporting of non-serious labeled adverse events like alopecia, Sanofi received a waiver from FDA in May 2000 stating that Taxotere-related periodic safety reports did not need to include copies of case reports for those events. (Sanofi_00259029). FDA

encourages sponsors to seek such waivers for non-serious labeled events. (FDA Draft Guidance for Industry, Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, March 2001).

94. Sanofi repeatedly evaluated cases of persistent, ongoing, or permanent alopecia it received either as spontaneous or literature reports or reported as part of the reporting requirements for ongoing clinical trials. Discussion of those cases is included in the periodic reports. In 2011 and 2015, Sanofi conducted signal analyses of persistent, ongoing, or permanent alopecia adverse event reports. These analyses are discussed below.

2011 Clinical Overview

95. In 2011 at the request of the French drug regulatory agency (AFSSAPS), Dr. Emanuel Palatinsky, the Taxotere Global Safety Officer for Sanofi, conducted a comprehensive signal assessment of “persistent” alopecia (Sanofi_02994797). Sanofi submitted these findings to FDA as part of PSUR 28 on January 27, 2011. (Sanofi_00201968; Sanofi_00197757).

96. For purposes of the analysis, a cumulative search was conducted in the Sanofi global pharmacovigilance adverse event database, using MedDRA version 13.1 to detect all cases, from all report sources, with the diagnosis of persistent alopecia associated with docetaxel. That search revealed a total of 1,620 cases, including solicited and unsolicited cases. Of the 1,620 potential cases of persistent alopecia, 1,060 of these reports were reported as having an unknown or unreported outcome, meaning these cases could not unequivocally be defined as cases of permanent alopecia. Of the remaining 560 cases of possible permanent alopecia, 348 cases were reported as Recovered/Recovering/Recovered with sequelae; 212 remaining reports of alopecia were reported as “Not recovered”. There were 142 cases which could be determined to meet the definition of “persistent alopecia”, meaning hair loss persisting for 12 months or

longer following the last dose of chemotherapy. Further analysis of these 142 cases revealed 24 reports of persistent alopecia that did not have sufficient information to allow a medical assessment of the reports as potentially related to docetaxel.

97. After a careful review of these cases, Sanofi concluded that there is no evidence of a causal relationship between docetaxel and persistent alopecia and that “the available evidence does not show that irreversible alopecia is caused by docetaxel alone.” This conclusion was supported by the fact that the cases were confounded by (1) exposure to multiple anticancer agents each known to cause alopecia; (2) multiple co-morbidities associated with the onset of alopecia; (3) lag time between the last dose of docetaxel and the onset of alopecia greater than two months; (4) the onset of alopecia predated the first administration of docetaxel; or (5) persistent alopecia was reported as resolved in three patients who did not have characteristics differing from other patients where the alopecia was reported as irreversible.

98. Contrary to the claims of Plaintiffs’ regulatory expert (Kessler Report at para. 190), this 2011 clinical overview was submitted both to FDA and the European Medicines Agency (“EMA”). FDA did not respond to or require any labeling changes based on the clinical overview. FDA could have followed-up with Sanofi or requested revised labeling, but did not do so. The EMA reviewed the clinical overview and agreed with Sanofi’s conclusion that “On the basis of this safety review, it is effectively difficult to conclude that docetaxel alone is able to induce persistent alopecia.” (Sanofi_01113662). That said, the European Rapporteur recommended an update to the European label to address the possible risk of persistent alopecia more clearly. (Sanofi_01113662). In September 2011, Sanofi proposed additions to the Taxotere Summary of Product Characteristics, specifically a statement that “Cases of persistent alopecia have been reported” in the Undesirable Effects postmarketing section and a statement in

the patient information that “Hair loss (in most cases hair growth should resume).”

(Sanofi_01112272, Sanofi_05413055). This change was endorsed by the European health authority in December 2011. (Sanofi_00813022).

2015 Response to Agency and 2015 Clinical Overview

99. On March 23, 2015, Frank Cross, Jr., Senior Regulatory Health Project Manager at FDA, emailed Sanofi and requested “a summary of cases of permanent partial or total alopecia associated with docetaxel use.” Sanofi provided its response to FDA on April 10, 2015.

(Sanofi_00265619). In preparing its response, Sanofi conducted a cumulative search of its Global Pharmacovigilance adverse event database using MedDRA version 17.1 to detect cases reported from any source included a diagnosis using the high-level term “alopecia.”

(Sanofi_00265624). A total of 89 cases reported the verbatim term “alopecia” and the word “permanent” or “irreversible,” or reported alopecia persisting for more than two years with the outcome of Not Recovered/Recovering/UNK. Sanofi provided a summary of those cases to FDA. Most cases were female patients with breast cancer and the majority of patients were treated with combination anticancer treatments. Sanofi concluded that “alopecia occurs very commonly. Permanent alopecia is mostly reported in the female patients with breast cancer. The available evidence does not show that permanent alopecia is caused by docetaxel alone.”

100. Approximately six months later, on October 2, 2015, FDA provided its response to Sanofi’s April submission. FDA requested that Sanofi “[p]rovide any additional information regarding permanent or irreversible alopecia” and “[a]mend the package insert in Section 6.2 (Postmarketing Experience) (and patient information, if appropriate) to add information on permanent or irreversible alopecia.” (Sanofi_00805353).

101. On November 24, 2015 Sanofi provided FDA with its response to this request entitled “Clinical Overview: Docetaxel and Permanent Alopecia”. (Sanofi_03333249). The Clinical Overview evaluated the potential association between docetaxel and permanent alopecia and included a Changes Being Effected labeling supplement proposing to update both the Postmarketing Experiences section of the USPI and the patient labeling with information on permanent alopecia.

102. In this Clinical Overview, Sanofi provided background information on docetaxel, alopecia, the incidence of alopecia with anti-cancer agents and an updated review of its global pharmacovigilance database. (Sanofi_01268143). Sanofi identified 117 cases of alopecia that included either “permanent” or “irreversible,” as descriptors or that reported alopecia lasting more than two years and with an outcome of Not Recovered/Recovering/Unknown. Again, the vast majority of cases were female patients treated for breast cancer, and 70% of the cases received confirmed combination chemotherapy regimens. Sanofi provided to FDA a summary of these cases and its analysis of the 117 cases, along with results from the TAX 316 and GEICAM 9805 studies, and the results from its literature review.

103. Sanofi wrote that “the cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia in the patients who received docetaxel.” Sanofi concluded that “[t]he positive causal association between docetaxel and permanent/irreversible alopecia does not affect the benefit-risk relationship. Docetaxel has been widely used and proven effective as a chemotherapeutic agent. The benefits of docetaxel continue to outweigh the risks, including permanent alopecia.”

104. In my opinion, Sanofi provided a thorough analysis of the available postmarket and clinical trials data on alopecia. FDA generally does not require or encourage sponsors to

make causality assessments based on postmarket data. Sanofi's use of certain phrases should not be construed as an unequivocal statement of causality, especially in light of their proposed labeling changes. Further, I believe that the data analyses are complicated by the absence of an established and widely agreed upon case definition for "permanent alopecia", by case-patient exposure to other chemotherapeutic agents known to cause alopecia, and by the practical limitations of using postmarket data to make causality assessments. Thus, the reading of the language in the Clinical Overview must be tempered by consideration of the significant limitations in using postmarket case reports for assessing causality.

105. Therefore, while I understand that Plaintiffs use Sanofi's 2015 Clinical Overview to assert that Sanofi concluded that docetaxel causes permanent alopecia, I believe that this is inappropriate for the reasons listed above. To me, Sanofi's conclusion means that, based on the available data and a possible biological explanation for alopecia following docetaxel exposure, Sanofi's pharmacovigilance department determined that the cumulative evidence could support a potential relationship between Taxotere exposure and the reported cases of permanent alopecia, but not to the exclusion of other causes. (Jen Deposition, September 21, 2018, pp. 385-386, Hangai Deposition, February 1, 2018, pp. 18, 194, 275-276.). Because of other confounding factors, such as use of previous and concomitant medications (such as doxorubicin, cyclophosphamide, etc.), age, family history, possible Tamoxifen use and other factors, Sanofi did not and could not conclude that docetaxel causes permanent alopecia.

106. My view is consistent with FDA's review of the 2015 Clinical Overview. After reviewing the Sanofi overview, FDA's Medical Reviewer stated: "The Sponsor and FDA concur that the available evidence supports a **potential** causal association between docetaxel and permanent alopecia and that the label should be updated to alert clinicians and patients of this

possibility.” (NDA 20-449, s-075, Medical Review, Prowell, T., December 7, 2015) (emphasis added). The same FDA Medical Reviewer also stated: “In 70% of these reported cases, patients had received docetaxel as part of combination chemotherapy, so it’s impossible to determine whether the permanence of alopecia was due to docetaxel, which may have implications for labeling of numerous cytotoxic agents. In any case, I think the Sponsor’s simple statement that permanent cases have been reported is all that can reliably be said given the tremendous limitations of the available data.” (2015 Prowell, T. to Diggs, F., et al., Congressional Response Letter – Taxotere Adverse Events, December 4, 2015). If a positive causal assessment had actually been made, the labeled language update could have reflected that conclusion. It did not.

TAXOTERE CLINICAL TRIALS

107. Taxotere was initially approved as a single agent chemotherapy regimen for the treatment of metastatic anthracycline/anthracenedione resistant breast cancer. Metastatic breast cancer is cancer that has spread to other parts of the body. Anthracycline or anthracenedione resistant breast cancer is cancer that has progressed despite treatment with what was at that time the most effective and most commonly used chemotherapeutic agent for the treatment of breast cancer. The four phase II clinical trials that formed the basis for this initial approval were multi-center, active-control clinical studies. A total of 162 patients were enrolled, 134 of whom were documented as treatment resistant due to a lack of response or progression of disease on treatment. The four pivotal trials were conducted in the U.S. (83 patients) and in Europe (79). Five additional phase II studies enrolling a total of 154 patients and conducted primarily outside the U.S provided additional supporting documentation of Taxotere’s effectiveness and safety profile. The overall response rate in this population of women with advanced breast cancer ranged from 35% to 68%.

TAX 316

108. In 2004, FDA approved docetaxel as adjuvant therapy for operable, node-positive breast cancer based on the findings from the TAX 316 study. The TAX 316 study (also known as EFC6041/BCIRG001), is “A multicenter phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) as adjuvant treatment of operable breast cancer patients with positive axillary lymph nodes.”

109. The primary objective of the TAX 316 study was to compare disease-free survival (DFS) in operable breast cancer patients with positive axillary lymph nodes after treatment with Taxotere (docetaxel) combined with doxorubicin and cyclophosphamide (TAC) versus disease free survival following treatment with 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC). The secondary goals were to compare overall survival (OS), toxicity, and quality of life between the two treatment arms and to evaluate pathologic and molecular markers for predicting efficacy.

110. Sanofi worked closely with FDA in designing and executing the TAX 316 study. As FDA notes in its Medical Review of the TAX 316 second interim analysis, the protocol for the study was submitted to FDA on August 13, 1997, in full compliance with the principles of the Declaration of Helsinki. (Sanofi_01254309). The statistical analysis plan as well as subsequent TAX 316 protocol amendments were submitted to, reviewed and approved by FDA prior to implementation. (Sanofi_01254309). FDA was actively involved in all aspects of protocol development and modification.

111. I agree with FDA’s assessment of the efficacy and safety profile demonstrated by the TAX 316 study. In reviewing the TAX 316 second interim analysis, FDA’s Medical

Reviewers concluded that “the docetaxel (TAC) arm demonstrated statistically significant and clinically relevant superiority in the traditional oncology endpoint of interest in the treatment of adjuvant breast cancer (disease free survival), and also prolonged survival as measured against an accepted control arm (FAC).” (Sanofi_012554305). In addition, FDA concluded that “[t]he safety profile of Docetaxel given as a combination therapy is consistent with the toxicities described in the label for the individual study drugs.” (Sanofi_01254307).

112. Similar efficacy and safety results were reported in the final clinical study report for TAX 316, completed in September 2010. The final results from the TAX 316 10-year follow-up “continue to support the use of TAC as an appropriate adjuvant chemotherapy option in women with operable, node-positive breast cancer.” (Sanofi_02649521).

113. With respect to “ongoing alopecia,” there were 29 cases (4.2%) in the TAC arm and 16 (2.5%) cases in the FAC arm from the TAX 316 final clinical study report. These results do not constitute a signal of an increased risk for an association between TAC and “ongoing alopecia” as there is not a statistically significant difference between the incidence of “ongoing alopecia” in the two arms.

114. I have reviewed the protocols, statistical analysis plan, and clinical study reports for the TAX 316 study. It is my opinion that this trial was appropriately designed and conducted. It is also my opinion that the results of the TAX 316 study, both the 2004 interim analysis and the 2009 final analysis, were appropriately submitted to FDA in compliance with federal regulations and good regulatory practices.

115. Sanofi could not have conducted a clinical trial with a primary endpoint of permanent or irreversible alopecia. As stated earlier in my report, long-term safety studies with adverse events as primary endpoints are not required and generally are not considered to be

ethical study designs. That is true here. It would not have been an ethical study design to have a clinical trial administering docetaxel in cancer patients using permanent or irreversible alopecia as the primary endpoint, especially considering the severity of the disease for which the drug was developed and approved. To propose such a study would be absurd.

116. Plaintiffs claim that the results of the TAX 316 study provide support for the proposition that docetaxel causes permanent alopecia. For a number of reasons, that is incorrect. First, as I've already stated, there were reports of "ongoing" alopecia in both the Taxotere and non-Taxotere arms of the study, meaning that patients who were not administered Taxotere also reported to have "ongoing" alopecia. Importantly, there was not a statistically significant difference between the incidence of "ongoing alopecia" in the TAC as compared to the FAC arm of the study. In addition, alopecia is not an unexpected event with virtually all types of chemotherapy. Based on the TAX 316 study, it is impossible to say that there was a meaningful difference in the rates of ongoing alopecia between the two arms of that study.

117. Second, the TAX 316 study only reported "ongoing" alopecia; it did not report "permanent" or "persistent" alopecia. The distinction is important, since for the majority of patients identified as having "ongoing" alopecia, there is no documentation that those patients had alopecia lasting more than six months after completion of chemotherapy. (Deposition of Michael Kopreski, M.D., 10/11/18, pp. 737-759; Ex. A to Sanofi's Responses to Plaintiffs' Notice of 30(b)(6) Deposition - Table of TAX316 Patients).

118. Third, all patients who were recorded as having persistent alopecia were also treated with doxorubicin and cyclophosphamide, both of which are associated with reports of persistent alopecia in the absence of concurrent Taxotere treatment. (See Masidonski, Pat, and Suzanne M. Mahon. "Permanent alopecia in women being treated for breast cancer." *Clinical*

journal of oncology nursing 13.1 (2009): 13-14; Yagata, Hiroshi, et al. "Abstract P5-15-17: National survey of long-term recovery from chemotherapy-induced hair loss in patients with breast cancer." (2015): P5-15).

119. I have reviewed the analysis of the TAX 316 final data performed by Dr. Michael Kopreski, an oncologist and former manager in Sanofi's pharmacovigilance department. Dr. Kopreski concludes that of the 29 patients who received Taxotere and were identified as having "ongoing" alopecia, only six had any evidence of alopecia more than six months after chemotherapy. For the remaining 23 patients, there was simply a report of alopecia into the follow-up period, reporting which may have occurred as soon as three months following chemotherapy treatment. It is important to note again that alopecia following cancer chemotherapy is not unexpected and certainly does not constitute, at 3 months post treatment, "permanent" or "irreversible" alopecia. Similarly, of the 16 patients who received the FAC regimen, and were reported with "ongoing" alopecia, only three had evidence of alopecia more than six months after chemotherapy.

120. It is therefore simply incorrect for Plaintiffs' experts to suggest that the results of the TAX 316 study demonstrate that approximately 4% of Taxotere patients experience "permanent" or "irreversible" alopecia. In actuality, fewer than 1% of the Taxotere patients in the TAX 316 study had alopecia more than six months after chemotherapy.

121. Dr. Kopreski explained that of the 744 patients who received Taxotere, 29 were identified as having evidence of "ongoing" alopecia at the end of the study. However, "ongoing" does not mean the same as "persistent", as it has been defined by Plaintiffs' experts. (Kopreski Dep. Tr. at 725:12–15.) Instead, "ongoing" simply means that the last time the patient was

assessed, the patient had some degree of hair loss, or alopecia. *See* Kopreski Dep. Tr. at 725:16–19.

122. In order to determine how many of the 29 identified cases of “ongoing” alopecia in the TAC arm had evidence of “persistent” alopecia as it has been defined, Dr. Kopreski closely reviewed the TAX 316 study. Dr. Kopreski’s criteria for finding “persistent” alopecia—rather than “ongoing” alopecia—was simple. *See* Kopreski Dep. Tr. at 729:9–11. Dr. Kopreski looked at how many patients had documentation of alopecia six months after their last chemotherapy treatment, and whether there was documentation of the alopecia’s subsequent resolution. *See* Kopreski Dep. Tr. at 729:7–18. If a patient had documentation of alopecia six months after chemotherapy, without evidence of subsequent resolution, Dr. Kopreski considered that patient to have persistent alopecia. *See* Kopreski Dep. Tr. at 729:22–730:3.

123. Applying this criterion, Dr. Kopreski identified only 6 of the 29 patients with reported “ongoing” alopecia to have evidence of “persistent” alopecia. (Ex. A to Sanofi’s Responses to Plaintiffs’ Notice of 30(b)(6) Deposition - Table of TAX316 Patients). Importantly, Dr. Kopreski considered these patients to have persistent alopecia regardless of whether the patient was taking another drug, such as Tamoxifen, which could have been affecting the lack of hair regrowth. *See* Kopreski Dep. Tr. at 730:1–3.

124. When the actual TAX 316 patient data is reviewed, it becomes apparent that such data does not support a finding of causation for persistent alopecia and Taxotere exposure. For example, patient 15002 is one of the 29 patients in the TAC arm with “ongoing” alopecia. That patient received one cycle of TAC, administered on 8/26/98. (Sanofi_02649521, p.7383). The patient developed alopecia after this treatment cycle. (Sanofi_05503627). She was withdrawn from the study after developing gastrointestinal mucositis following TAC administration.

(Sanofi_02649521, p.343). On 9/23/98 the patient began alternative chemotherapy treatment with AC. (Sanofi_05503640). At her first follow up visit on 11/3/98, alopecia was recorded as ongoing and “No longer followed due to new chemotherapy regimen started.”

(Sanofi_05503639, 05503641). No further alopecia assessments were made for this patient. After a distant breast cancer relapse, the patient began treatment with Taxol on 8/31/99. (Sanofi_05503649). She was lost to follow up since 12/22/99. (Sanofi_05503594) and was recorded as deceased due to breast cancer on an unknown day in 8/01. (Sanofi_05503655).

125. Similarly, patient 15006 is one of the 29 patients in the TAC arm with “ongoing” alopecia. That patient received one cycle of TAC, administered on 12/23/98. The patient developed alopecia after this treatment cycle. (Sanofi_05503700). She was withdrawn from the study after developing anaphylaxis during TAC administration. (Sanofi_002649521, p.344). On 1/12/99 the patient began alternative chemotherapy treatment with AC. (Sanofi_05503707). At her first follow up visit on 2/23/99, alopecia was recorded as ongoing and “No longer followed due to new chemotherapy regimen started.” (Sanofi_05503711, 05503716). No further alopecia assessments were made for this patient. After a distant breast cancer relapse, the patient began treatment with vinorelbine on 8/10/99. (Sanofi_05503719).

126. For these reasons, the results of the TAX 316 study cannot be used to determine that docetaxel causes permanent hair loss. The results of the TAX 316 study instead demonstrate less than a 1% rate of alopecia six months after chemotherapy, based on the carefully reviewed available information. Even in that 1%, it is impossible to rule out other potential causes of the patients’ absence of full and complete hair regrowth after chemotherapy, including the co-administration of other chemotherapeutic agents among the reports of permanent alopecia.

GEICAM 9805

127. The GEICAM 9805 study (also known as TAX.ESI.301) was “A multicenter Phase 3 randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) as adjuvant treatment of high risk, operable breast cancer patients with negative axillary lymph nodes.”

128. The primary goal of the study was a comparison of disease-free survival after adjuvant treatment with either TAC or FAC among patients with high risk, operable breast cancer and negative axillary lymph nodes. The secondary goals were to compare overall survival, toxicity, and quality of life between the two groups, and to evaluate pathologic markers for predicting efficacy.

129. The first patient was enrolled in the study on June 21, 1999 and the final report cut-off date for patients followed for at least 5 years was March 4, 2009. The follow-up report cut-off date was April 22, 2013.

130. The clinical study report, dated September 15, 2009, reported that TAC was associated with a statistically significantly 32% reduction in the rate of relapse as compared to FAC. There was also a non-significant improvement in overall survival with TAC compared to FAC. (Sanofi_00724383). The safety profile of TAC was consistent with the known toxicity of the individual drugs and the TAC combination and was consistent with the toxicity findings of the TAX 316 study. (Sanofi_00724385).

131. The same report noted in the analysis of TEAEs persisting into the follow-up period that “alopecia remained ongoing in 3 of 49 (6.1%) of TAC patients compared with 1 of 35 (2.9%) FAC patients.” (Sanofi_00724490).

132. On November 30, 2009, Sanofi submitted the results of GEICAM 9805 as a supplemental NDA s-060 to FDA for the new indication of adjuvant chemotherapy among patients with high risk, operable breast cancer and negative axillary lymph nodes. As part of s-060, Sanofi also provided its proposed changes to the Taxotere label, reflecting the findings from GEICAM 9805. As it had done with the 2004 TAX 316 submission, Sanofi proposed adding to the Adverse Reactions section of the USPI the subsection “**Other persistent reactions...**The following events were observed to be ongoing in TAC-treated patients at the median follow-up time of 77 months; alopecia (n=3/49), amenorrhea (n=7/18), lymphoedema (4/5), peripheral sensory neuropathy (3/10).” (Sanofi_00384656).

133. After a number of discussions with FDA, Sanofi withdrew the GEICAM 9805 efficacy supplement, citing changes in the standards of care for high-risk node-negative breast cancer patients from the time the GEICAM 9805 study was initiated in 1999 to when the efficacy supplement was filed in 2009. (Sanofi_03242136).

EPIDEMIOLOGY AND CAUSATION

134. Epidemiology is the study of the patterns of disease in populations. Epidemiologic studies record the outcomes and exposures of individuals, using specific study designs and statistical methods to estimate the risk of disease associated with an exposure or other potential risk factor. The statistical analyses estimate the uncertainty in that correlation and can serve to estimate the likelihood that such a correlation may be causal.

135. In estimating the risk of a disease associated with an exposure, certain epidemiologic data and studies are considered to be more reliable than other types of information. The gold standard for estimating health effects associated with a specific exposure is the prospectively designed, randomized, placebo-controlled, adequately powered clinical trial – an

epidemiologic study where a specific exposure, like a pharmaceutical agent, is randomly assigned to the selected population of enrolled human subjects. Random assignment of one or more exposure within the patient population is intended to distribute the potential for benefit randomly within the identified study population. As noted above, it is not ethical to design or conduct clinical trials in order to determine risk alone. In terms of estimating risks for uncommon conditions like persistent/permanent hair loss, observational studies that follow participants in clinical trials over time or registries that enroll large numbers of individuals receiving the treatment of interest are generally more useful than other forms of non-clinical evidence such as animal studies and in vitro testing or expert opinion. Prospectively designed epidemiologic studies can provide population-based information on risks in an exposed human population with similar overall risk factors such as similar rates of a variety of underlying illnesses. Thus, the risk of an uncommon outcome like persistent alopecia can be estimated. Such studies cannot prove causation, but can be useful in estimating risks with identified exposures and reported illnesses or medical conditions.

136. There is a widely accepted “hierarchy of evidence” that is used by virtually all scientific bodies charged with determining the outcomes of exposures or the causes of disease. This hierarchy is described in the Reference Manual on Scientific Evidence (3rd edition) published jointly by the Federal Judicial Center and the National Academy of Sciences as a guide for courts in evaluating the strength and validity of scientific evidence. It is reflected in the following paragraph from that document:

Hierarchy of medical evidence

With the explosion of available medical evidence, increased emphasis has been placed on assembling, evaluating, and interpreting medical research evidence. A fundamental principle of evidence-based medicine (see also Section IV.C.5, infra) is that the strength of medical evidence supporting a therapy or strategy is

hierarchical. When ordered from strongest to weakest, systematic review of randomized trials (meta-analysis) is at the top, followed by single randomized trials, systematic reviews of observational studies, single observational studies, physiological studies, and unsystematic clinical observations.¹ [Reference Manual, 3rd Edition, P. 723].

137. I have reviewed the causation opinions of Plaintiffs' experts and note that Plaintiffs' experts reach their causation opinions in large part by relying on case reports. Case reports are the lowest and least reliable for of scientific evidence. Case reports generally have little evidentiary value in establishing general causation. Case reports are often confounded (*i.e.*, the case involves an adverse event that has possible etiologies other than the product of concern), are often missing information, may be subject to reporting or attribution bias and lack any comparison group. That is why FDA has stated:

For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-controls studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.

FDA Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

138. Plaintiffs' experts also rely on analyses of the FAERS database used by FDA. As stated earlier in my report, spontaneous adverse event reporting is designed to raise questions to be investigated in formal epidemiologic studies. Spontaneous reports are more often than not incomplete, are notoriously under-reported to FDA or other postmarket surveillance databases, and can be influenced by litigation or publicity. Use of FAERS data to make causal inferences is not generally considered scientifically reliable.

139. Based on my review of the available scientific evidence, plaintiffs' experts' causation claims are unreliable. It is my opinion that the currently available scientific evidence does not support an unequivocal causal role for Taxotere alone in persistent or permanent alopecia. As noted by FDA, the data are too confounded to make such an assertion.

CONCLUSIONS

140. FDA reviewed and analyzed a tremendous amount of data related to the safety and efficacy of Taxotere. In accordance with its regulations, FDA's overall positive assessment of Taxotere is reflected in its repeated approvals of new indications, in Taxotere's being granted accelerated approval status for several indications, and in labeling that shows no change to the safety profile of the product, particularly concerning the risk of persistent/permanent alopecia.

141. Sanofi and FDA have appropriately evaluated the safety and effectiveness data for Taxotere throughout product development, during the approval processes, and through careful postmarket safety surveillance. The labeling has been repeatedly updated to reflect new safety and effectiveness data, as needed. Sanofi's postmarket studies and safety surveillance of Taxotere is consistent with the good pharmacovigilance and pharmacoepidemiologic assessments and practices recommended by FDA. Sanofi complied with FDA regulations and with industry standards in its review and submission of information supporting its NDA and sNDAs. Through its postmarket safety submissions, labeling submissions, and clinical study submissions, Sanofi repeatedly and appropriately shared the information it had on alopecia with FDA.

142. FDA analyzed relevant safety and effectiveness data during the development, approval and postmarket surveillance of Taxotere. Both premarket and postmarket scientists and regulatory personnel were involved in the review of these data. FDA's regulatory decisions were

based on a thorough and attentive appraisal of the data for Taxotere. FDA clearly relied on its experience and resources for drug product decision-making in general, including drug product approval and labeling as well as its experience and knowledge of both Taxotere specifically and of taxanes more generally. Sanofi conducted appropriate studies of Taxotere after marketing approval in order to further evaluate the efficacy and safety of the product. The doctor and patient labeling for Taxotere have at all times complied with FDA regulations and provided the essential information to patients and prescribers for the safe and effective use of the product.

REVIEW OF PLAINTIFFS' EXPERTS' REPORTS

143. Before addressing the specifics of Plaintiffs' experts' reports, it should be noted that Plaintiffs' experts conflate reports of alopecia with reports of "permanent" or "irreversible" alopecia. This conflation is present in their analysis of the clinical trial data, the adverse event data, and of the medical literature. After treating reports of alopecia as if they were reports of "permanent" or "irreversible" alopecia, Plaintiffs' experts conclude that there was a "safety signal" for Taxotere and permanent or irreversible alopecia, that Taxotere may pose an increased risk of permanent or irreversible alopecia apart from other breast cancer chemotherapeutic agents, and that Taxotere may have been the more consistent or likely cause of alopecia among patients exposed to Taxotere for the treatment of the cancers for which it is approved. None of these opinions are reliably drawn due in large part to the experts' conflating of alopecia with permanent or irreversible alopecia.

144. As stated earlier in my report, alopecia is not an unexpected event in approved breast cancer chemotherapy. Alopecia is not an unexpected event in clinical trials evaluating proposed new chemotherapy agents for use in treating breast cancer. With virtually every chemotherapeutic agent used or proposed for use in treating breast cancer, and in any clinical

study of the same, there are likely to be reports of alopecia during treatment, during the study, and in follow up. In the simplest of terms, patients in clinical trials for the treatment of breast are likely to experience some degree of alopecia, either before the study begins due to prior chemotherapy treatment or during the trial. They may experience slow or incomplete hair regrowth after completing the trial. There may be great variability in the rate of hair regrowth following completion of the trial and they may experience changes in their hair following chemotherapy as compared to prior to chemotherapy.

145. There is uncertainty in the precise meaning of “ongoing” and “persistent” in regard to adverse events that may occur in the clinical trial context. Whether an adverse event is ongoing or persistent is measured at a fixed period in time and may not be measured again if a patient drops out of a trial or completes the trial and does not return for follow-up specifically to address the presence of a particular adverse event, like hair loss or alopecia. For those patients, reports of an “ongoing” or “persistent” adverse event does not mean that hair loss was “irreversible” or “permanent.”

146. None of the adverse event reports or clinical study data can appropriately be characterized as cases of “permanent” or “irreversible” alopecia, let alone connected to chemotherapy at the exclusion of other causes, without such specific clinical evaluation. Sibaud et al. made this point in observing that the terms “CIPAL” or “PCIA” should not include the term “permanent” because no long term, controlled studies have been performed which specify continued evaluation and documentation of the degree or duration of alopecia among breast cancer patients in clinical trials and the final clinical outcome of most reports is unknown. (V Sibaud, et al., Dermatological adverse events with taxane chemotherapy, Eur. J. Dermatol. (2016) Oct. 1; 26(5); 427-443).

David Madigan, Ph.D.

147. I have reviewed Dr. Madigan’s Report entitled “Docetaxel and Irreversible Alopecia”. Among other tasks, Dr. Madigan claims to address the question of whether a safety signal was present for docetaxel and “irreversible alopecia” and when a signal might have appeared. He claims to have reviewed Sanofi’s internal pharmacovigilance database “in relation to docetaxel and irreversible alopecia” and he claims to have performed various statistical analyses of clinical trials data.

148. First, I will address the issue of a safety signal for “irreversible alopecia”, which appears to be confined to breast cancer patients treated with docetaxel in combination with other cancer chemotherapy agents.

149. Dr. Madigan acknowledges many of the well-known limitations in the use of spontaneously reported postmarket adverse events reports, including incomplete reports, under-reporting of adverse events by physicians and others, and includes FDA’s own statement that “[c]aution must be exercised in evaluating spontaneous reports, especially when comparing drugs.” As further noted in the quoted FDA Guidance, “...AERS...data may be affected by the submission of incomplete or duplicate reports, under-reporting, *or reporting stimulated by publicity or litigation*. As reporting biases may differ by product and change over time ... it is not possible to predict their impact on data mining scores.” (emphasis added) (FDA Guidance: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Mar. 2005) (<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf>.) The guidance goes on to indicate that “many other factors affect the reporting rate of product-related adverse events (e.g., publicity, newness of the product to the market) and these factors should be considered when interpreting a high reporting rate.” (2005 Guidance at

page 12. *See also Pharmacoepidemiology* 5th edition; B Strom Ed. Wiley-Blackwell publisher; page 151 and van Hunsel F, van Puijenbroek E, van den Berg LD; van Grootheest K. Media attention and the influence on reporting odds ratio in disproportionality analysis: An example of patient reporting of statins. *Pharmacoepidemiol Drug Safe.* 2010; 19: 26-32). In its 2005 Guidance FDA recommends that “sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events.” Further discussion indicates the need to estimate reporting rates using U.S. cases as a numerator and estimates of national patient exposure to the product as the denominator.

150. With that brief background on methodology and the limitations of spontaneously reported adverse event data, I want to respond to some of Dr. Madigan’s statements. First, signals cannot be used to establish causality. For the reasons noted above, patient and physician reporting of adverse events is affected by a number of unquantifiable biases including recency of product approval and publicity concerning a specific adverse event.

151. Dr. Madigan cites the 2005 Guidance for the proposition that “[c]omparisons of reporting rates and their temporal trends can be valuable...” but fails to incorporate the subsequent cautionary comment: “However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used”. Dr. Madigan offers no estimated denominator in his comparisons of reporting rates for docetaxel as compared to paclitaxel or other cancer chemotherapeutic agents nor does he address that while these chemotherapy agents are all used to treat malignancies, their spectrum of usage and duration of time on the U.S. market are widely divergent, further undermining the validity of his comparative reporting rates assessments. This does not mean that there are not differential reporting rates and that comparisons might be informative, but it

does mean that any interpretation of those rates must be viewed with great caution due to uncertainty about the effect of factors that might affecting report rates, like notoriety or recency of approval. (FDA Guidance: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment at 4 (Mar. 2005)).

(<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf>).

152. Dr. Madigan claims in paragraph 28 of his report that he “removed duplicates defined as having identical manufacturer and control codes” (sic). Matching reports with identical manufacturer control numbers (MCN) does not address the problem of duplicate reports. It may identify the initial and subsequent or follow-up reports but will not detect truly duplicated reports. Duplicate reports may arise from more than one person submitting a report on the same patient and same adverse event or submitting the same report to different entities, such as FDA and the manufacturer. Duplicate reports are eliminated by reviewing each report to identify the same patient and event being reported two or more times by different reporters or to different databases. For example, a physician, nurse, patient or patient relative each might submit separate reports for the same individual. Or a prescribing physician might submit a report both to FDA and the manufacturer. It is by comparing age, gender, location and other factors that one eliminates duplicates, not via the simple expediency of matching MCNs. Dr. Madigan does not appear to appreciate the complexity and care needed to accurately review and assess adverse event reports prior to conducting statistical “analyses”.

153. FDA has frequently made the point that the most reliable adverse event reports are those received from healthcare providers, particularly physicians. While Dr. Madigan

indicates that the excluded reports from lawyers (paragraph 30), he does not discuss reports from other sources such as consumers.

154. In his section 4, entitled “Docetaxel FAERS Analysis”, Dr. Madigan describes his statistical analysis of adverse event reports for docetaxel which he describes as indicating the presence of a clinical entity he refers to as “irreversible alopecia”. First, there is no such term in the MedDRA coding system, which FDA and other regulatory agencies and entities use for the purpose of coding reported adverse events. He claims to have defined this clinical entity he calls “irreversible alopecia” by combining the MedDRA term “Alopecia” with the outcome of “Disability or Permanent Damage”. Unfortunately, it is not clear whether he reviewed the retrieved reports to be certain that alopecia was the only reported adverse event. If there were other events included in the report, there would be no way to be certain that the outcome of “Disability or Permanent Damage” referred to alopecia or some other adverse event term. It is not at all clear that his methodology as described would have resulted in identification of cases of alopecia that were coded by the reporter as resulting in disability or permanent damage. Thus, his case identification methodology appears to either be flawed or poorly described.

155. Dr. Madigan’s disregard of the potential influence of either litigation or notoriety (e.g. web-based support group entitled “Taxotears”) is a glaring deficiency in his methodology. Despite his identification of published material discounting the effect that publicity of various sorts may have on adverse event reporting, it is clear that there is a visible inflection point in the 2009 – 2010 timeframe, which is neither acknowledged nor evaluated by Dr. Madigan in his report. This is the putative timeframe in which the Taxotears web group became active, promoting the allegations of excessive numbers of patients with permanent alopecia after receiving combination cancer chemotherapy that included Taxotere. To ignore this inflection

point runs counter to FDA's assessment of such inflection points as indicating stimulated reporting. Stimulated reporting renders the FAERS or other spontaneously reported adverse event databases useless in assessing comparative reporting rates.

(Pariante, A., Gregoire, F., et al, Impact of Safety Alerts on Measures of Disproportionality in Spontaneous Reporting Databases: The Notoriety Bias, Drug Safety, 891 (2007); FDA, Executive Summary Memorandum, Metal-on-Metal Hip Implant Systems, Appendix I: Summary of Medical Device Adverse Event Reports (June 27-28, 2012 at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM309406.pdf>), Hazell and Shakir pg. 386). In addition, the absence of an estimated denominator further hampers a fuller interpretation of the adverse event reporting data in Dr. Madigan's analyses.

David Kessler, J.D., M.D.

156. I have reviewed Dr. Kessler's report in this matter. Dr. Kessler is insistent that alopecia can be considered a serious adverse event under the FDA regulations (21 C.F.R. 312 or 314.80). I disagree. While patients may report that the failure of their hair to regrow or regrow either completely or in a manner indistinguishable from hair growth, distribution, texture or other characteristics of their pre-cancer chemotherapy hair, FDA has clearly not determined that this type of incomplete hair regrowth or persistent alopecia is a serious adverse event under its regulations. FDA has not instructed Sanofi or other taxane manufacturers to place such information on alopecia in the Warnings and Precautions section. Information on alopecia appears in the Clinical Trials, Postmarketing Adverse Events, Patient Counseling and the Patient Package insert sections of the product labeling. Despite Dr. Kessler's personal opinion, it is clear that the regulators at FDA, whose job it is review and approve prescription drug labeling

including the Taxotere labeling, do not agree. As noted in the preamble to the new labeling regulations (FR Vol.71 No, 15 January 24, 2006 Final Notice January 24, 2006; page 3968):

FDA carefully controls the content of prescription drug labeling, because such labeling is FDA's principal tool for educating health care practitioners about the risks and benefits of the approved product to help ensure safe and effective use. As FDA noted in the preamble accompanying the December 2000 proposed rule amending the 1979 physician labeling regulations:

The part of a prescription drug product's approved labeling directed to health care practitioners * * * is the primary mechanism through which FDA and drug manufacturers communicate essential; science-based prescribing information to health care professionals. This part of approved labeling is a compilation of information based on a thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant *** [T]he primary purpose of prescription drug labeling is to provide practitioners with the essential information they need to prescribe the drug safely and effectively for the care of patients."

157. Further clarification of the appropriate information to be included in the Warnings and Precautions section is provided in the for the new Structured Product Labeling regulations (id page 3988):

(c)(6) *Warnings and precautions.* i. *General.* This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification).

158. I believe that this simple fact – that persistent alopecia is not considered to be a serious adverse event under FDA's regulations by FDA reviewers and regulatory personnel and obviously is not appropriate for inclusion in the *Warnings and precautions* section – renders further discussion of Dr. Kessler's theses on alopecia and the Taxotere labeling merely moot and not of substance.

159. At his deposition, Dr. Kessler placed significant emphasis on a 2006 abstract for a poster presentation by Dr. SM. Sedlacek, suggesting that the abstract should have required that Sanofi update the Taxotere labeling. (Kessler Deposition, December 20, 2018, p. 253). I disagree. Sanofi submitted to FDA the cases of “persistent alopecia” identified in the Sedlacek abstract and those cases were part of Sanofi’s 2011 Clinical Overview (Palatinsky Deposition, August 9, 2018, p. 300). Therefore, FDA was aware of the specific cases which were the subject of the abstract. While the Sedlacek abstract is relevant to the subject of Sanofi’s pharmacovigilance practices and regulatory reporting, the limited data available, the off-label nature of his treatment regimen, and the absence of a peer-reviewed publication providing further detail about these patients limits its utility and reliability.

160. Dr. Kessler’s Section X, which is a discussion of “Sanofi’s Marketing and promotional efforts to differentiate Taxotere versus Taxol/paclitaxel misled physicians and doctors and put patients at an increased risk of harm”, is of no regulatory significance. Internal marketing discussion are not regulatory documents and have no relevance to FDA’s actions unless those documents are translated into actual promotional/marketing materials or statements. As an aside, I am somewhat confused by the inclusion of both physicians and doctors in the title of his section X, as though doctors and physicians are two different classes of prescribers. However, apart from the marketing and promotional materials actually used in print, verbal or other representations, such documents and presentations do not constitute a regulatory record and will not be further addressed in this report.

Laura Plunkett, Ph.D.

161. In response to the expert report of Dr. Plunkett, I refer back to the patient labeling for Taxotere. From initial approval through 2010, the patient package insert stated that alopecia

was a common side effect of Taxotere treatment and that “hair generally grows back”, clearly indicating that hair does not grow back in all cases. FDA’s reasoning for removing that clause is not clear. The Agency provided no rationale. In 2004, based on TAX 316, Sanofi added a section to the Adverse Reactions section of the physician’s package insert entitled “Other Persistent Reactions”, which would have included peripheral neuropathy, alopecia, amenorrhea, peripheral edema, lymphedema, asthenia, and myelodysplastic syndrome/acute myeloid leukemia. As noted above, FDA’s Ann Staten removed this labeling addition without comment. Sanofi repeatedly evaluated its clinical trials data as well as its postmarketing data and submitted those evaluations and the data to FDA. The suggestions and claims by Drs. Plunkett and Kessler that Sanofi failed to inform physicians (and doctors) of the risk of persistent alopecia or hair loss is simply not true. Sanofi provided information in its labeling indicating that hair does not always grow back. In at least two instances, FDA removed that specific language without indicating the reasoning behind its deletions. This fact again renders the allegations by Drs. Plunkett and Kessler moot in that the question was answered by FDA and Sanofi was required to comply with FDA’s decisions on labeling in order to legally market Taxotere in the U.S.

162. I hold these opinions to a reasonable degree of medical, scientific and regulatory probability. I reserve the right to respond to additional Plaintiff expert reports, rebuttal reports, deposition or trial testimony.

Janet Arrowsmith, M.D.

Janet B. Arrowsmith, M.D.
Corrales New Mexico

EXHIBIT M

Filed Under Seal

EXHIBIT M

Expert Report
Justin R. Victoria

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December 28, 2018

I, Justin R. Victoria, have been retained as an expert in the Taxotere litigation by sanofi-aventis U.S. LLC and Sanofi US Services Inc. (Sanofi). If asked, I am prepared to testify at trial regarding the matters set forth in this report.

I. Qualifications

Since November of 2009, I have served as the founder and owner of JR Victoria Consulting LLC, a consulting firm specializing in providing advice to healthcare companies on regulatory affairs issues, including the design and implementation of regulatory compliant product development programs to facilitate regulatory review and approval, financial communication issues, and pharmaceutical product litigation.

Before beginning my consulting work, I worked for 32 years in the pharmaceutical industry in the United States, including nearly twenty years in positions of increasing responsibility and functional leadership in regulatory affairs, two years in project management, and nine years in a leadership position in Investor Relations.

I received a Bachelor of Science degree in Biochemistry from Rensselaer Polytechnic Institute in Troy, New York in 1976. I received a Master of Science degree in Biochemistry from the State University of New York at Buffalo in 1977 based upon work at the Roswell Park Memorial Cancer Research Institute. I also received a Master of Business Administration degree in Pharmaceutical Marketing and Management from Fairleigh Dickinson University in Teaneck, New Jersey in 1983.

I started working in the pharmaceutical industry in 1977 at Hoffmann La-Roche (Roche), where my initial position was in basic research in immunology. In 1978, I transferred to a

clinical research position at Roche, where I contributed to the design of clinical studies, monitored conduct of the trials at the investigator sites in the field, and participated in interpretation and reporting of the resulting clinical data, leading to the approval of New Drug Applications (NDAs) by the United States Food and Drug Administration (FDA) for new therapies.

In 1980, I transferred to the Regulatory Affairs department at Roche. My initial position was that of a Technical Coordinator where I had responsibility to review and transmit biomedical data to the FDA in accordance with the relevant Investigational New Drug (IND) and NDA regulations. I had responsibility for direct communication and follow-up with the FDA to resolve any inquiries associated with such filings. Over the course of the next four years, I gained additional responsibilities in regulatory affairs at Roche, progressing to the lead position for the Anti-Infective work team in the department, where I had full regulatory responsibility for products in this category.

In 1984, I transferred to the Regulatory Affairs department of Ayerst Laboratories (Ayerst Laboratories was a Division of American Home Products in New York, NY. It was subsequently combined with another division, Wyeth Laboratories, in 1988 to form Wyeth-Ayerst Laboratories in Philadelphia, PA. The parent, American Home Products was later renamed Wyeth, then based in Madison, NJ.), where I served as regulatory liaison for several therapeutic categories of investigational and marketed prescription drug products and the Ayerst line of over-the-counter (OTC) drug products.

In 1988, I transferred to the newly combined Wyeth-Ayerst Laboratories in Philadelphia, PA and by 1989 I was promoted to the position of Director, U.S. Regulatory Affairs, when I assumed leadership of the regulatory affairs function for all Wyeth-Ayerst domestic products, including investigational products, products pending review and marketed products. In this role, I was responsible for supervision and oversight of a staff of approximately 50 regulatory professionals and the associated administrative staff. I was the senior-most regulatory officer for Wyeth-Ayerst responsible for FDA liaison, including direct communications with senior leadership at FDA. During my tenure in regulatory affairs, I participated in dozens of meetings with FDA, serving as the chair for Wyeth-Ayerst in many. I continued in that role until 1995.

For a two-year period in 1995-1996, I was assigned to lead the Project Management department for Wyeth-Ayerst, to oversee the coordination of the global development projects for the Wyeth-Ayerst Research and Development (R&D) portfolio. In this role, I was responsible for portfolio management of the R&D projects, including selection of projects for development and prioritization among development projects.

In 1997, I returned to leadership of the domestic regulatory effort at Wyeth-Ayerst, adding responsibility for oversight of the worldwide regulatory function in 1998. In the worldwide regulatory function, I was responsible for the direct oversight of a staff of 180 regulatory professionals who managed the regulatory responsibilities for products in more than 130 countries around the world. In addition to direct interface with senior officials at FDA, when I assumed responsibility for worldwide regulatory affairs, I interacted with senior regulatory officials at the European Medicines Agency (EMA), the European Committee for Proprietary Medicinal Products (CPMP), the Canadian Health Protection Branch (HPB) and other national health authorities.

During my tenure in regulatory affairs at Ayerst/Wyeth-Ayerst, I was directly and personally involved with the regulatory activities associated with dozens of investigational compounds and I contributed to the approval of more than two dozen new drugs in multiple therapeutic categories.

I was responsible for making submissions to FDA for investigational and marketed compounds and interacting with FDA officials on such filings to ensure they were found acceptable for review. I advised company functions on regulatory requirements to develop and market products in a fashion consistent with regulations and FDA guidelines and policies. I contributed to company training programs in that regard.

I was responsible for review of proposed promotional materials to ensure such materials were compliant with FDA regulations and the policies and practices of the Division of Drug Marketing, Advertising and Communications (DDMAC). In that capacity, I served on Wyeth-Ayerst Copy Clearance Committees and the Copy Clearance Executive Committee, collaborating with representatives of legal, medical and marketing to ensure the truthfulness, scientific/medical accuracy and regulatory compliance of proposed promotional materials. I was involved in preclearance of introductory promotional

campaigns, both professional and direct-to-consumer (DTC), by DDMAC for a number of products. I was also responsible for communications and resolution of issues raised by DDMAC relating to Wyeth-Ayerst promotional materials.

I collaborated with medical staff at Wyeth-Ayerst on decisions relating to regulatory requirements for reporting of safety information, including safety reports on investigational drugs, and Adverse Drug Experience (ADE) reports and Periodic Adverse Drug Experience Reports (PADERS) for marketed products.

I was involved in developing initial product labeling during NDA submission, review and approval, and subsequent labeling updates, including regulatory decision-making as to the appropriate filing strategy for labeling changes. In that regard, I participated in various labeling committees at Wyeth-Ayerst.

I participated in preparing for and presenting to FDA Advisory Committees.

I developed a scientific understanding to contribute to discussions of clinical, pharmacokinetic, chemistry, pharmacologic, toxicologic and statistical issues with company and FDA staff.

During the course of my tenure in regulatory affairs, I was an active, contributing member to regulatory professional societies including the Regulatory Affairs Professionals Society (RAPS), The Drug Information Association (DIA), the Food and Drug Law Institute (FDLI) and the Delaware Valley Regulatory Affairs Forum (DVRAF), presenting on various topics relating to regulatory affairs and FDA processes.

Based upon my experience in the regulatory affairs area, I am familiar with FDA regulations, procedures and policies, the underlying food and drug law, and the obligations, responsibilities and practices of regulated pharmaceutical companies.

During my tenure at Ayerst/Wyeth-Ayerst, I also served on several R&D oversight committees responsible for guiding drug discovery, drug development, and overall R&D portfolio management efforts. On these committees, I contributed to discussions and evaluation of preclinical studies and data to determine whether to transition investigational

compounds into clinical development, choices of development projects and pathways to NDA filing and approval, and portfolio emphasis between new and life-cycle projects.

In 2000, I become Vice President of Investor Relations at Wyeth. In that role, I was responsible for communications with investors and securities analysts, describing financial and operational performance and future opportunities at Wyeth to address questions for investment decision-making. Oftentimes, these questions related to drug development and regulatory issues. During my tenure in Investor Relations, I continued to serve as an active member of Wyeth R&D governance committees, overseeing the clinical progress of compounds in development and the status of FDA review, and contributing to decision-making relating to the overall portfolio of R&D projects.

My current resume, which describes my qualifications and professional experience in greater detail, is attached as Exhibit A. A list of the testimony I have given in the last seven years is attached as Exhibit B.

II. Materials Reviewed

A listing of the materials reviewed in the preparation of this report is attached as Exhibit C together with any other materials specifically referenced in the body of this report.

The materials include documents related to the development, review, labeling and promotion of Taxotere, transcripts and exhibits from depositions, and materials related to the regulation of prescription drug development, labeling and promotion.

I have also reviewed the expert report of David Madigan, Ph. D. dated November 2, 2018, the expert report of Laura Plunkett, Ph. D. dated November 4, 2018 and the expert report of David Kessler, M.D. dated November 6, 2018.

III. FDA Regulations and Role in Development, Approval, and Labeling of Prescription Drugs

A. Overview of FDA and Its Role in Drug Development

1. The FDA

The FDA is responsible for protecting the US public health by assuring the safety, efficacy, and security of human and veterinary drugs, vaccines and other biological products, medical devices, the food supply, cosmetics, and products that emit radiation, and by regulating the manufacture, marketing, and distribution of tobacco products. The FDA is also responsible for helping healthcare professionals and the public get the accurate, science-based information they need to use medicines and foods to improve health. To meet these responsibilities, FDA has a staff of over 16,000 personnel and an annual operating budget of nearly \$5 billion.¹

FDA's organization consists of the Office of the Commissioner and four groups overseeing the core functions of the agency: Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, and Operations.

Within the abovementioned Office of Medical Products and Tobacco, the Center for Drug Evaluation and Research (CDER) is the organization within FDA responsible for ensuring that safe and effective drugs are made available to the American public. The FDA's authority to do so comes from the Federal Food, Drug, and Cosmetic Act of 1938 (the Act) and its subsequent amendments. FDA promulgates regulations, policy statements, guidelines, guidances and other pronouncements to guide the pharmaceutical industry and other stakeholders in how to implement the specific provisions of the Act. FDA, through CDER, has the responsibility to review and approve new drugs and for post-approval oversight of marketed drugs. FDA's authority over drug products includes drugs under development but not yet approved, as well as drugs that have been approved by FDA.

¹ <https://www.hhs.gov/about/budget/fy2017/budget-in-brief/fda/index.html#overview>.

2. New Drug Development and Regulatory Review Processes

The process to bring a new drug to market is a complex, highly regulated and time consuming one. In brief, drug companies seeking approval to sell a drug in the United States must test it in a number of ways. First, the drug company or sponsor performs laboratory and animal tests to discover how the drug works and whether it's likely to be safe and work well in humans. Next, a series of tests in humans is begun to determine whether the drug is safe when used to treat a disease and whether it provides a valid health benefit. The company then sends the results of these tests to FDA in a New Drug Application (NDA)² so that the agency can evaluate the drug. The NDA review process can take from six to twelve months or longer to complete. If this review establishes that a drug's health benefits outweigh its known risks, the drug is approved for sale and the manufacturer may make it available to the market in the United States, consistent with the FDA-approved labeling.

Looking at this process in more depth, the first step in identifying new compounds to treat a disease or condition in the discovery process is to develop an understanding about the underlying cause of the disease or condition. Researchers must first identify a "target," (usually a gene or protein), determine if the target can interact with drug candidates, and confirm that it is involved in the disease through the conduct of laboratory and animal tests ("target validation"). Researchers then synthesize many compounds to be tested to find potential "lead compounds" that act on the target and that may alter the course of the disease. The lead compounds are subjected to a series of additional exploratory tests to evaluate the "activity" of the compound, or how well the compound binds to and acts on the target.

Following the synthesis of potential drug candidates, the next stage of the drug development process is preclinical testing. During preclinical testing, researchers evaluate a drug development candidate's pharmacologic,³ pharmacokinetic,⁴ and toxicological effects through in vitro ("within the glass," i.e., in a test tube or petri dish-laboratory tests) and in vivo (animal models) testing.

² 21 CFR 314.

³ Pharmacological activity refers to the effects of a compound, preferably the desired activity, in living systems.

⁴ Pharmacokinetics is how the organism handles and processes a drug after its administration.

Researchers perform early toxicity tests to determine whether the compound is toxic or potentially carcinogenic and to identify the doses at which the compound first shows indicators of toxicity and what these signs of toxicity are.

Short-term animal studies are then used to test the efficacy or effectiveness of the compound in affecting the disease or condition in animal models in what is termed preclinical pharmacology. Depending on the target, after the early exploratory laboratory studies, researchers may test efficacy in a succession of animal models, including mice, rats, dogs, and other mammals. Evidence of the desired effect in animal models is needed to support continued development.

Researchers later perform a series of longer-duration pharmacokinetic, toxicologic and pharmacologic tests in a progression of animal models, still within the preclinical testing phase. These tests define the drug development candidate's "therapeutic window," or the range of dosages that are both effective and safe. Ideally, a drug development candidate will exhibit a wide therapeutic window in multiple animal models (i.e. a large range of doses that show effectiveness with few, if any, indicators of toxicity until higher doses are achieved). Severe side effects, side effects at the therapeutic dose (narrow therapeutic window), early indications of carcinogenic potential, or poor or inconsistent pharmacokinetics across species can all derail development of a drug candidate at this stage.

During the preclinical development stage, researchers also study how the lead compound may be formulated into a drug product for delivery to humans. The physiochemical properties of a drug candidate dictate the drug's potential to be put into a stable dosage form in which it can be consumed and delivered as an effective drug. For example, researchers test for solubility, compatibility with inactive ingredients, and stability. The drug product must be stable to provide the defined dose after storage in adverse conditions. The dosage form must be acceptable to patients (e.g. palatable). The dosage form must be able to be consistently manufactured at large scale. Lack of success in any of those factors can serve as a reason to discontinue the development of a drug candidate.

The discovery and preclinical development processes are long, costly, complex and highly challenging. In a 2006 study of the drug discovery, development and review processes by

the United States Government Accountability Office (GAO),⁵ the GAO projected that only five compounds would successfully proceed into clinical trials from 10,000 compounds initially screened for the drug discovery and preclinical testing processes. That represents a probability of success of 0.05% or the converse rate of failure of 99.95%. This process is not only likely to yield failure, it is also time consuming in that the average time of the discovery and preclinical development processes collectively is about 6.5 years before trials in humans can even begin.

If all of the preclinical drug development has proceeded successfully, the Investigational New Drug Application (IND)⁶ is filed by the company that will take responsibility for developing a drug (the sponsor) to show the FDA the results of preclinical testing they've done in laboratory animals and what they propose to do for human testing. At this stage, the FDA decides whether it is reasonably safe for the company to move forward with testing the drug in humans.

These tests in humans to develop the data necessary to evaluate the safety and effectiveness of drugs prior to marketing of a new product in the United States are divided into three phases. Phase 1 studies⁷ are usually conducted in healthy volunteers. The goal here is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted. The number of participants typically ranges from 20 to 80.

Phase 2 studies⁸ begin if Phase 1 studies don't reveal unacceptable safety risks. While the emphasis in Phase 1 is on safety, the emphasis in Phase 2 is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people whom have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment--usually an inactive substance (placebo), or a different drug. Safety continues to be evaluated, and short-term side effects are studied. Typically, the number of patients in Phase 2 studies ranges from a few dozen to about 300.

⁵ United States Government Accountability Office, New Drug Development 8, available at <http://www.gao.gov/new.items/d0749.pdf>.

⁶ 21 CFR 312.

⁷ 21 CFR 312.21(a).

⁸ 21 CFR 312.21(b).

Phase 3 studies⁹ begin if evidence of effectiveness is shown in Phase 2. These studies gather more information about safety and effectiveness, studying different populations and different dosages and using the drug in combination with other drugs. The number of patients usually ranges from several hundred to about 3,000 people or more.

As described in the abovementioned GAO report, the clinical development of a new drug, encompassing Phase 1, 2 and 3 studies, typically takes about seven years to complete.¹⁰ Once the data from these clinical studies are collected and analyzed, the company files a New Drug Application (NDA).¹¹ This is the formal step a drug sponsor takes to ask that the FDA consider approving a new drug for marketing in the United States. FDA regulations define the required content and structure of the submission of an NDA.¹² An NDA includes the animal and human data from studies conducted by the sponsor or from other sources (e.g., published scientific literature) and analyses of the data, as well as information about how the drug behaves in the body, how it is manufactured and an initial proposal from the manufacturer for product labeling.

3. **FDA Review of an NDA**

When an NDA is submitted, the FDA has 60 days to decide whether to file it so that it can be reviewed.¹³ The FDA can refuse to file an application¹⁴ that is incomplete or not formatted in a fashion that will permit its review. For example, some required studies might be missing.

Once a new drug application is filed, an FDA review team from the various divisions within the Office of New Drugs (OND) within CDER--medical doctors, chemists, statisticians, microbiologists, pharmacologists, epidemiologists, supervisory review officers, Division Directors, Office Directors and other experts--evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use. No drug is absolutely safe; all drugs have side effects. "Safe" in this sense means that the benefits of the

⁹ 21 CFR 312.21(c).

¹⁰ GAO 2006 at 8.

¹¹ 21 CFR 314.

¹² 21 CFR 314.50.

¹³ 21 CFR 314.101.

¹⁴ 21 CFR 314.101(d).

drug appear to outweigh the risks.

In certain instances, FDA calls upon external resources to review the safety and efficacy of a proposed new drug in the form of an FDA Advisory Committee. The Advisory Committee is principally comprised of medical experts in the relevant field and they recommend approval or disapproval of a drug's marketing application.¹⁵ For oncology drugs such as Taxotere, the relevant advisory committee is the Oncologic Drugs Advisory Committee (ODAC). ODAC "reviews and evaluates data concerning the safety and effectiveness of marketed and investigational drug products for use in the treatment of cancer and makes appropriate recommendations to the Commissioner of Food and Drugs."¹⁶

In addition to the data and information submitted by the sponsor in the NDA, the FDA reviewers will also rely on other information that may be relevant to their review of the drug in question such as the published scientific and medical literature. Also, importantly, for a drug such as Taxotere, FDA will also call upon its historical knowledge of the development, clinical studies, safety profile, and post-marketing surveillance of similar drugs in the same therapeutic class. This knowledge forms a foundation to which the reviewers compare a new entry to the therapeutic class, such as Taxotere, to ensure that the benefit/risk ratio of the new product is acceptable. This was done in comparing the therapeutic profile of Taxotere with the previously approved drug Taxol by the FDA reviewers and the FDA Advisory Committee in their consideration of Taxotere for approval in 1994 – 1996 as will be discussed later in this report.

The review team analyzes study results and looks for possible issues with the application, such as weaknesses of the study design or analyses of the underlying data. The review process can take from six to twelve months or longer to complete. There are usually many communications back and forth between FDA and the sponsor¹⁷ to clarify information and to provide additional information to allow for FDA to complete its review of the application. Reviewers determine whether they agree with the sponsor's results and conclusions, or

¹⁵

<https://www.fda.gov/advisorycommittees/committeesmeetingmaterials/drugs/default.htm>.

¹⁶

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/default.htm>.

¹⁷ 21 CFR 314.102.

whether they need any additional information to make a decision.

Each reviewer prepares a written evaluation containing conclusions and recommendations about the application. The clinical review is described in a Medical Officer Review (MOR). These evaluations are then considered by team leaders, division directors, and office directors, depending on the type of application for a consensus decision on the approvability of the application.

As FDA considers whether the benefits of a drug outweigh the risks, if there are problems with the NDA or if more information is necessary to make that determination, the FDA may issue a complete response letter.¹⁸

Common issues in the review of an NDA that would be cited in a complete review letter include unexpected safety issues that crop up or failure to demonstrate a drug's effectiveness. A sponsor may need to conduct additional studies--perhaps studies of more patients, different types of patients, or for a longer period of time. FDA can refuse to approve the drug until those studies are done to address any questions about its safety or effectiveness.

If there are such questions to be resolved, the FDA outlines these issues and the justification for its decision on an NDA in the complete response letter to the drug sponsor and CDER gives the sponsor a chance to meet with agency officials to discuss the deficiencies. At that point, the sponsor can choose to ask for a hearing, or correct any deficiencies and submit new information, or they can withdraw the application.

If upon completion of its review, FDA finds that the data contained in the NDA provides evidence of the drug's safety and substantial evidence of its effectiveness for its proposed use from adequate and well-controlled clinical trials, it approves the NDA and permits the marketing and distribution of the drug in the US.

The process through clinical development and FDA review leading to approval and the market entry of a new drug product in the United States is challenging, unpredictable and fraught with uncertainty. The early indications of success from animal models often are not

¹⁸ 21 CFR 314.110.

good predictors of success in humans. In oncology drug development this is particularly noteworthy. Noted authorities in the field have observed that positive studies in animals have not been reflective of safety and efficacy in man on numerous occasions. Dr. Richard Klausner of the National Cancer Institute has commented, “The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades, and it simply didn’t work in humans.”¹⁹ Additionally, a safe and effective dosing regimen has to be identified and confirmed in the clinical studies. Few drugs that begin development actually succeed in receiving NDA approval. For instance, the 2006 report on drug development by the GAO referenced above found that only 1 in 5 drugs that make it to the clinical trials phase is ultimately successful in completing all three clinical testing phases.²⁰ A more recent 2014 report by the Tufts Center for the Study of Drug Development reports that the success rate of drugs and biologics from Phase 1 through marketing approval is less than 12 percent.²¹ The most recent data from the KMR Group as reported by Dr. Tim Anderson of Bernstein (characterized as “best-in-class data because the input come directly from the companies themselves”) was that it takes 11.8 phase 1 compounds to yield one marketed product, for a success rate of 8.5%.²² Thus, from 80% to as many as 93% of the drugs entering clinical trials fail to reach market, demonstrating how daunting the process of clinical development and regulatory review is.

The information in this section of the report has described a standard FDA NDA review process. Because the standard processes for development and FDA review of a new drug are time-consuming, the FDA has developed mechanisms to expedite drug development and approval to make therapeutically significant drugs for serious diseases available earlier.²³ These mechanisms include Breakthrough Therapy status, Fast Track status, Priority Review and Accelerated Approval.²⁴ These approaches to drug development and approval work in different ways and are applicable at different times in the process, but they do not relax the rigorous standards for efficacy and safety needed for drug approval in the U.S. Substantial

¹⁹ <http://askuswhy.com/cancer.htm>.

²⁰ GAO 2006 at 7.

²¹ Tufts Center for the Study of Drug Development, Briefing: Cost of Developing a New Drug 17, November 18, 2004.

²² Bernstein, Global Pharmaceuticals: Ten charts on latest R&D productivity trends – the most important fundamental attribute, November 28, 2017.

²³ <https://www.fda.gov/ForPatients/Approvals/Fast/default.htm>.

²⁴ Ibid.

evidence of effectiveness and safety from adequate and well-controlled clinical studies is still required to be presented to FDA to support drug approval. The Accelerated Approval process is oftentimes used in the first-time approval of new therapies for oncology²⁵ as that process allows for drugs for serious conditions (cancers) that fill an unmet medical need to be approved based on a surrogate endpoint (e.g., tumor response) that is reasonably likely to predict clinical benefit, such that FDA may approve these drugs and make them available to treat cancer patients faster than they might otherwise.²⁶ FDA then requires confirmatory clinical studies to demonstrate that the evidence of effect on the surrogate endpoint is ultimately verified in clinical benefit (e.g., survival benefit).²⁷ Approval of the drug may be withdrawn or the labeled indication changed if the follow-up trials fail to verify the clinical benefit.²⁸ As will be discussed later in this report, the initial FDA approval of Taxotere in May 1996 for advanced breast cancer was via the accelerated approval process.²⁹

4. FDA Review of Labeling

During the review of the NDA, the FDA also reviews the sponsor's proposed draft labeling for the product and makes revisions to the language to ensure that the labeling contains accurate information reflecting the data obtained from the clinical trials and other sources of clinical data, is consistent with labeling regulations, and provides adequate directions for use and warnings about the use of the drug. Those labeling revisions are discussed with the sponsor, with final labeling text determined by FDA at the time of approval. The goal is to ensure that the scientific and medical information available to both the medical/scientific experts of the sponsor and FDA, and the judgment of both as to how to best characterize that information in the framework of the FDA labeling regulations, are considered. If FDA does not agree with the sponsor on the specific labeling language, it will not approve the labeling and, thus, not approve the drug.

In order for the new drug to be approved for marketing in the United States, the FDA must determine that the data contained in the NDA provides evidence of the drug's safety and

²⁵ Johnson, J., et. al., *Accelerated Approval of Oncology Products: The Food and Drug Administration Experience*, J Natl Cancer Inst 2011;103: 1-9.

²⁶ <https://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm>.

²⁷ Ibid.

²⁸ Ibid.

²⁹ Sanofi_01380011-15.

substantial evidence of its effectiveness for use from adequate and well-controlled clinical trials,³⁰ and that the labeling contains a summary of the essential scientific information needed for the safe and effective use of the drug.³¹ If these standards are met, and there are no other reasons to deny approval, FDA approves the NDA³², approves the labeling and, thus, approves the drug for market. As will be described in the next section of the report below, FDA then continues to review the adequacy of the labeling throughout the life of the product in the market. FDA recognizes that a drug's labeling cannot contain everything that is known about a drug. Such labeling would be too voluminous to be useful.³³ It is meant to provide a summary of the actions of the drug in humans and relevant safety, efficacy and use information so that a health professional can appropriately weigh the benefits and risks of the drug for individual patients.³⁴

5. Post-Marketing Surveillance

After the drug is approved, the FDA continues to monitor a drug's safety profile and the adequacy of its labeling. This is done by the medical experts in the Office of New Drugs that originally reviewed the NDA, as well as experts from the Office of Surveillance and Epidemiology (OSE), a group trained specifically to evaluate information relating to the safety of drug products. FDA has the authority to require changes to a drug's labeling after it is approved, just as it does before approval. If the sponsor does not make the required changes to the labeling, FDA could consider the drug misbranded and subject to regulatory action, including removal from the market.

To facilitate this oversight, the sponsor continues to monitor the safety of the drug in the marketplace and provides post-approval update reports to FDA.^{35,36} In an NDA Annual Report³⁷ the sponsor is to summarize significant new information that it has received or otherwise obtained during the previous year that might affect the safety, effectiveness or

³⁰ 21 CFR 314.126.

³¹ 21 CFR 201.56.

³² 21 CFR 314.125.

³³ Guidance for Industry – Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, January 2006, pp. 2, 5.

³⁴ 21 CFR 201.56(a).

³⁵ 21 CFR 314.80.

³⁶ 21 CFR 314.81.

³⁷ 21 CFR 314.81(b)(2).

labeling of the drug product, and to describe the actions it intends to take; for example, to submit a change to the labeling via a supplemental application – sNDA.³⁸ The NDA Annual report is to provide distribution data and describe any authorized generic products,³⁹ as well as Chemistry, Manufacturing and Controls information about the physical drug itself.⁴⁰ Internal or published reports of nonclinical laboratory (animal) studies are to be included.⁴¹ Additionally, the sponsor is to monitor the published literature about its drug and provide published clinical studies and reports of unpublished (sponsor) clinical studies, providing FDA with an update on available clinical data on the drug after its review of the original NDA.⁴² Copies of current labeling and a description of changes in labeling since the last report are to be included.⁴³ Thus, even in the absence of changes to the labeling in the course of the year, the sponsor resubmits its labeling to FDA for its consideration on at least an annual basis. Lastly, the NDA Annual Report is to include a status report of post-marketing study commitments and a log of outstanding regulatory business.⁴⁴

Safety information for marketed prescription drug products is handled in its own unique process. All safety information from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers is to be collected, assessed and submitted by the sponsor in accordance with the FDA regulations at 21 CFR 314.80. The safety information is evaluated by the manufacturer for safety “signals”: new potential associations between drug products and adverse events. Reports of adverse drug experiences from domestic and foreign postmarketing experience (spontaneous reports), from post-marketing clinical studies or from the scientific literature that are serious and unexpected (not labeled) are to be reported to FDA on an expedited (15-day) basis.⁴⁵ Accordingly, the FDA-approved US product label serves as the reference of “expectedness” for post-approval safety assessments under 21 CFR 314.80.

³⁸ 21 CFR 314.81.

³⁹ 21 CFR 314.81(b)(2)(ii).

⁴⁰ 21 CFR 314.81 (b)(2)(iv).

⁴¹ 21 CFR 314.81 (b)(2)(v).

⁴² 21 CFR 314.81(b)(2)(vi).

⁴³ 21 CFR 314.81 (b)(2)(iii).

⁴⁴ 21 CFR 314.81(b)(2)(vii) and (viii) and (ix).

⁴⁵ 21 CFR 314.80(c)(1) and 314.80(d).

The post-marketing safety reporting regulations also call for follow-up investigation and reports of such serious and unexpected adverse experiences to be submitted on an expedited, 15-day basis.⁴⁶ FDA clarifies this requirement in its various guidances on this topic. “FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment , . . . especially for serious events.”⁴⁷ “FDA suggests that the intensity and method of case follow-up be driven by the seriousness of the event reported, the report’s origin , . . . and other factors. FDA recommends that the most aggressive follow-up efforts be directed towards serious adverse event reports, especially of adverse events not known to occur with the drug.”⁴⁸ “For serious adverse experiences, applicants should exercise due diligence in obtaining follow-up information for the purposes of completing all the applicable elements for an individual case safety report. For adverse experiences that are determined to be non-serious... additional follow-up is not necessary.”⁴⁹ Thus, FDA considers that good pharmacovigilance practices will include follow-up investigation and reporting for serious and principally unlabeled adverse events, not for non-serious events, employing good medical and pharmacovigilance judgment.

Additionally, the sponsor is to summarize and analyze postmarketing safety information in a Periodic Adverse Drug Experience Report (PADER).⁵⁰ PADERs are to be submitted on a quarterly basis for the first three years after a drug is approved and then annually thereafter.⁵¹ The PADER is to include a summary and analysis of all the included safety information, an analysis of the reports of serious and unexpected adverse drug experiences submitted since the previous PADER, an index and individual case study reports for all serious and expected, and non-serious adverse drug experiences (reports of serious and expected, and all non-serious adverse drug experiences from foreign marketing experience,

⁴⁶ 21 CFR 314.80(c)(1)(ii).

⁴⁷ Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005, p. 4.

⁴⁸ Ibid, p. 5.

⁴⁹ Guidance for Industry, Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, Draft Guidance, March 2001, pp. 16.

⁵⁰ 21 CFR 314.80(c)(2).

⁵¹ 21 CFR 314.80(c)(2).

scientific literature and post-marketing studies are not to be reported to FDA⁵²) and a history of actions taken since the last PADER because of adverse experience reports (e.g., labeling changes).⁵³ FDA also encourages sponsors to seek a waiver of the requirement to include the individual case reports of the adverse experience reports for serious and expected, and all non-serious adverse drug experiences in the PADER.⁵⁴ Sanofi sought, and on May 25, 2000, FDA approved such a waiver for Taxotere such that the PADERs and PSURs would no longer include copies of case reports for adverse experiences that are non-serious and labeled.⁵⁵ Sanofi continued to provide case reports for adverse experiences that are serious and expected. If a sponsor fails to establish appropriate safety monitoring and record-keeping processes and/or does not make the appropriate safety reports outlined above, FDA may withdraw the NDA approval and prohibit continued marketing of the drug.⁵⁶

This process of post-marketing safety surveillance and reporting is called pharmacovigilance. Through this process, both the sponsor and FDA continue to monitor the safety of the use of the product in the marketplace to make sure the product labeling continues to provide adequate directions for the safe use of the product. If either the FDA or the sponsor determines that a change to the label is warranted, discussions as to the appropriate revisions to the labeling language ensue and a supplemental NDA is filed for FDA to approve the labeling change. [There is a provision in the regulations for a sponsor to submit a labeling change for FDA review, but to implement it immediately while the FDA review is ongoing via a Special Supplement – Changes Being Effectuated (CBE), for labeling changes that add or strengthen a contraindication, warning, precaution or adverse reaction for the product.⁵⁷ While FDA recognizes this provision in the labeling regulations, it notes that, “in practice, manufacturers typically consult with FDA prior to adding any risk information to labeling” since “the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA’s under the act.”⁵⁸ When the FDA review of the CBE

⁵² 21 CFR 314.80(c)(2)(iii), and Guidance for Industry, Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, Draft Guidance, March 2001, p. 20.

⁵³ 21 CFR 314.80(c)(2)(ii).

⁵⁴ Guidance for Industry, Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, Draft Guidance, March 2001, pp. 6, 15, 32.

⁵⁵ Sanofi_00259029.

⁵⁶ 21 CFR 314.80(k).

⁵⁷ 21 CFR 314.70(c)(6)(iii)(A).

⁵⁸ 71 FR 3934.

labeling change is completed, FDA may accept (approve) or reject the change. If FDA rejects the labeling change, the manufacturer will be required to return to the previous approved label in the market.]

To facilitate the global pharmacovigilance process, the International Conference on Harmonization (ICH), an initiative among the United States, European and Japanese regions to harmonize drug regulation across these three regions, implemented a guideline in 1996 to harmonize the periodic safety reporting requirement to the global regulatory authorities in a standard format called the Periodic Safety Update Report (PSUR).⁵⁹ The focus of the PSUR is on post-marketing safety information. With the finalization of this ICH guideline, FDA allowed sponsors to submit waivers to submit post-marketing safety reports under 21 CFR 314.80 in the format of a PSUR instead of the PADER format.⁶⁰ Sanofi sought, and on January 21, 2006, FDA approved such a waiver for the Taxotere NDA such that Sanofi submitted PSURs for Taxotere in place of Periodic Adverse Experience Reports from that point forward.⁶¹ The PSUR is to include:

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2.6.2 Cases presented as line listings

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⁵⁹ International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Periodic Benefit-Risk Evaluation Report (PBRER), E2C(R2), December 17, 2012, p. 1.

⁶⁰ Guidance for Industry, Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report), November 2016, p. 3.

⁶¹ Sanofi_00201968.

2.6.4 Summary tabulations

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2.8 Other Information

2.8.1 Efficacy-related information

2.8.2 Late-breaking information

2.9 Overall Safety Evaluation

2.10 Conclusion⁶²

While the ICH PSUR outline is more detailed than the regulatory description of the PADER, the primary purpose and content is much the same in requiring the sponsor to provide the regulatory authority with listings and reports of adverse experiences from post-marketing surveillance and reports from the published literature and the sponsor's analysis and evaluation of such reports to provide this periodic opportunity for an overall safety reevaluation.⁶³

To facilitate the evaluation of the post-marketing safety information by the global regulatory authorities, the PSUR guideline called for the sponsor to prepare a reference safety information document based upon the cumulative knowledge regarding the safety of the product called the Company Core Safety Information (CCSI). The CCSI facilitates the objective of a PSUR to establish whether information received during the reporting period is in accord with previous knowledge on the drug's safety and to determine whether changes should be made to product information.⁶⁴ Since product labeling can vary between the ICH regions, the CCSI provides a common reference source for the safety evaluation.

⁶² 62 FR 27472-75.

⁶³ 62 FR 27471.

⁶⁴ 62 FR 27472.

The CCSI is to contain a defined set of data and advice that the company intends to have reflected in the national labeling worldwide, except where the local regulatory authority requires a modification.^{65,66} The CCSI is not negotiated between the sponsor and the regulatory authorities.⁶⁷ Thus, the CCSI serves as an internal foundation or basis for safety-related labeling discussions between the local affiliates of the sponsor company and the local regulatory authority.⁶⁸ But, the local national regulatory agency retains the authority to determine the ultimate content of the local label. Thus, “Compared to the CCSI, the national/regional HP labeling may contain more, less or different safety information.”⁶⁹

Sanofi adopted the PSUR format for post-marketing safety reporting and included in its PSURs for docetaxel as the PSUR-required company Reference Safety Information, the Sanofi Company Core Safety Information including all the mandatory and non-mandatory safety information but also additional information such as the indications, dosing, pharmacokinetics and pharmacodynamics and information about the physical properties of the drug itself. [See for example Docetaxel Company Core Safety Information, Version 24, December 14, 2009.⁷⁰] The specific safety information content contained in the Sanofi docetaxel CCSIs is described later in this report.

The pharmacovigilance environment has evolved such that the regulatory authorities have recognized that the assessment of risks of drug products is most meaningful when considered in light of its benefits.⁷¹ Accordingly, the ICH has now expanded the PSUR to include benefits as well as risks in a new format called the Periodic Benefit-Risk Evaluation Report (PBRER).⁷² While the main focus of the PBRER remains the evaluation of relevant new safety information from the available data sources, this information is to be placed

⁶⁵ International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Periodic Benefit-Risk Evaluation Report (PBRER), E2C(R2), December 17, 2012, p. 26.

⁶⁶ MedDRA and Product Labeling: “Best Practices” Recommendations, MSSO-DI-8381-3.0.0, April 15, 2005, p. 2

⁶⁷ Ibid.

⁶⁸ Ibid.

⁶⁹ Ibid.

⁷⁰ Sanofi_00197905-44.

⁷¹ International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Periodic Benefit-Risk Evaluation Report (PBRER), E2C(R2), December 17, 2012, p. 1.

⁷² Ibid.

within the context of any pertinent efficacy/effectiveness information that may have become available since the last report.⁷³ Thus, the PBRER includes provisions for the reporting of efficacy/effectiveness information for benefit evaluation and a concluding integrated benefit/risk evaluation that was not part of the predecessor PSUR.

FDA has indicated its intent to accept the PBRER format as an acceptable approach for postmarketing periodic safety reports.⁷⁴ Sanofi sought, and on July 19, 2013, FDA approved such a waiver for the Taxotere NDA such that the Sanofi submitted PBERs for Taxotere in place of Periodic Adverse Experience Reports from that point forward.⁷⁵ The PBRER is to include:

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⁷³ Ibid, p. 3.

⁷⁴ Guidance for Industry, Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report), November 2016, p. 4-7.

⁷⁵ Sanofi_00268919.

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 - 18.2 Benefit-Risk Analysis Evaluation
- 19. Conclusions and Actions
- 20. Appendices⁷⁶

To allow for the inclusion of benefits in the supporting reference document to facilitate the benefit/risk evaluation of the PBRER, the CCSI has been expanded to include the approved indications for the product in the three ICH regions and information on dosing,

⁷⁶ International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use, ICH Harmonized Tripartite Guideline, Periodic Benefit-Risk Evaluation Report (PBRER), E2C(R2), December 17, 2012.

pharmacology and other issues beyond the core safety information in what is termed as a Company Core Data Sheet (CCDS).⁷⁷ As noted above, the Sanofi docetaxel CCSI already included such information.

a. FAERS Database

When the sponsor submits adverse experience reports (AERs) regarding its marketed drug products to FDA in accordance with its safety surveillance efforts described above, FDA enters this information into a database called the FDA Adverse Event Reporting System (FAERS).⁷⁸ FDA also receives reports of adverse events and medication errors directly from healthcare professionals such as physicians, nurses or pharmacists, or from consumers such as patients, family members or lawyers. These reports are also entered into FDA's FAERS database.

FDA utilizes the FAERS database in support of its efforts in post-marketing safety surveillance of drug products, such as looking for new safety concerns arising from the use of a drug product in the marketplace and responding to external requests for safety information. FAERS is a searchable tool for FDA in its postmarketing surveillance efforts. FDA reviewers in CDER evaluate reports from the FAERS database to determine if additional evaluation of a safety issue is required. This post-marketing surveillance of drugs in the marketplace continues at FDA throughout the life of the product.

While the FAERS is a useful tool to support FDA in its safety surveillance activities, it has limitations.⁷⁹ FDA does not require that a direct causal relationship between the reported event and the suspect drug be established before a report is submitted and entered into the FAERS database. Thus, there is no certainty that the reported event was actually due to the product. Reports also do not always contain enough detail to properly evaluate an event. Factors such as the time a product has been on the market, adverse events with similar products or publicity about a safety issue can all impact the reporting of adverse events to

⁷⁷ Ibid.

⁷⁸<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

⁷⁹

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

FDA. Additionally, there is a generally recognized bias of underreporting of adverse events, as FDA does not receive reports for every adverse event or medication error that occurs with a product. For these reasons and others, the FAERS data cannot be reliably used to calculate the incidence of an adverse event in the population nor can it be considered definitive in establishing the causal relationship between an adverse experience and a suspect drug.

b. Trackable Safety Issues

In January 2007, CDER launched a new information technology platform called the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) which allows CDER reviewers to share information, project plans, document reviews and recommendations for regulatory action across all disciplines within CDER.⁸⁰ DARRTS allows for a collaborative review of information about potential drug safety issues across CDER review disciplines. If the safety issue is determined to be a significant safety issue, one that has the potential to lead to:

- Withdrawal of an approved drug from the market
- Withdrawal of an approved indication
- Limitations on use in a specific population or subpopulation
- Additions or modifications to the Warnings and Precautions, or Contraindications sections of the labeling, or the Medication Guide or other required Patient Package Insert, including safety labeling changes required under the Food and Drug Administrative Amendments Act (FDAAA)
- Establishment of or changes to the proprietary name/container label/labeling/packaging to reduce the likelihood of medication errors
- Establishment or modification of a risk evaluation and mitigation strategy (REMS)
- A requirement that a sponsor conduct a safety-related postmarketing trial or study
- The conduct of a safety-related observational epidemiological study by FDA,

CDER then creates a Trackable Safety Issue (TSI) within DARRTS to follow the evaluation of

⁸⁰ Guidance – Classifying Significant Postmarketing Safety Issues, Draft Guidance, March 2012.

the issue throughout the Center.⁸¹ Such TSIs can be opened within DARRTS by the original NDA OND reviewers or by OSE staff based upon monitoring the FAERS database or other sources of postmarketing safety information. When a TSI is opened, the sponsor is notified and the public is subsequently notified through the posting of a quarterly listing of all new TSIs on the FDA AERS website.⁸²

Once the CDER reviewers complete their evaluation and determine what regulatory action is warranted, if any, then that action is implemented in concert with the drug manufacturer and the TSI is closed.⁸³

A recent example of a TSI posted on the AERS website is the finding from an FDA review of an international clinical study of oral fluconazole that demonstrated an increased risk of miscarriage.⁸⁴ FDA notes that its review of additional data is ongoing and that its conclusions and recommendations will be communicated when the evaluation is complete.

6. Advertising and Promotion

Another component of FDA's oversight of marketed prescription drug products is its surveillance of the advertising and promotion of such products to ensure that they are truthful, balanced, not misleading, and consistent with the FDA-approved labeling. Promotion and advertising that is regulated by the FDA include information that pharmaceutical companies generate and provide to healthcare professionals, such as physicians, and to consumers to educate about its products. Such promotional materials include, for example, brochures, mailing pieces, detailing pieces, advertisements in journals, newspapers, magazines and other periodicals, websites, and broadcast advertisements on

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<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm164967.pdf>.

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<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm248882.pdf>.

⁸³

<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm164967.pdf>.

⁸⁴ <http://www.fda.gov/Drugs/DrugSafety/ucm497482.htm>.

television, radio and through other electronic media.⁸⁵ A pharmaceutical company's requirements for compliance with the FDA advertising and promotion regulations relate to these and other types of promotional materials disseminated by or on behalf of the company.⁸⁶

Scientific and medical information discussing a particular disease or health condition that may be provided externally by sponsors, but which is not specific to a particular drug product (Unbranded or Disease-Awareness advertisements), are not considered promotional materials under these regulations.⁸⁷

The FDA prescription drug advertising regulations in 21 CFR Part 202 do not prescribe the specific content and presentation that is appropriate for promotional materials, but rather describe a more philosophical characterization of what promotional materials should not do. The basic tenet is that promotional materials should not be false, lacking in fair balance (of product benefits and risks) or be misleading.⁸⁸

Prescription drug advertising and promotion must present information about a drug to convey a "fair balance" of the benefits and risks of the use of the product."⁸⁹ The characterization of the benefits and risks is to be a "[t]rue statement of information in brief summary relating to side effects, contraindications, and effectiveness."⁹⁰

Promotional materials must be consistent with the information included in the FDA-approved labeling. This long-standing regulatory policy was recently confirmed in an FDA guidance.⁹¹ The words in the promotional materials are not required to be identical to the FDA-approved labeling.

⁸⁵ 21 CFR 202.1(l)(1) and (2).

⁸⁶ 21 CFR 202.1.

⁸⁷ Guidance for Industry – "Help-Seeking" and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms, Draft Guidance, January 2004, p. 1.

⁸⁸ 21 CFR 202.1(e).

⁸⁹ 21 CFR 202.1(e)(5)(ii).

⁹⁰ 21 CFR 202.1(e).

⁹¹ Guidance for Industry – Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers, Draft Guidance, January 2017.

Promotional materials may arise from any and all sections and information in the product label and the studies that support those sections of the labeling; however, the entire labeling information is not required to be included in the body of promotional pieces.⁹² For example, promotion can address, “Information about the onset of action of the product for its approved/cleared indication and dosing/use regimen,”⁹³ which would reflect the Clinical Pharmacology and Dosage and Administration sections of the labeling. Promotion can address, “product convenience”⁹⁴ which could reflect the Dosage Forms and Strengths and How Supplied sections of the labeling. The required “brief summary relating to side effects, contraindications,”⁹⁵ may include information from the Adverse Reactions and Contraindications sections of the labeling, but also the Warnings and Precautions, Limitations of Use, and potentially other labeling sections such as Pharmacokinetics, Drug Interactions, Use in Specific Populations, Overdosage, or Drug Abuse and Dependence. Also, “Advertising and promotion make frequent use of statements or data appearing in the CLINICAL STUDIES section.”⁹⁶ Essentially, any section of the prescription drug label may support promotional statements so long as such statements are consistent with that labeling section, are truthful and not misleading.

Promotional materials directed to physicians differ from those directed to consumers. For example, Direct-to-the Consumer (DTC) promotional materials should be written in consumer-friendly language.⁹⁷ DTC promotional materials for prescription drug products are designed to educate consumers and stimulate them to see their physician about their conditions and initiate a dialogue on treatment options, since only a healthcare professional can prescribe such products.

⁹² But either the full prescribing information (the label) or a “brief summary of Full Prescribing Information” with reference to the Full Prescribing Information accompanies written promotional materials.

⁹³ Guidance for Industry – Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers, Draft Guidance, January 2017, p. 6.

⁹⁴ *Ibid*, p. 7.

⁹⁵ 21 CFR 202.1(e)(1).

⁹⁶ Guidance for Industry – Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, January 2006, p. 11.

⁹⁷ Guidance for Industry – Brief Summary and Adequate Directions for Use: Disclosing Risk Information in Consumer-Directed Print Advertisements and Promotional Labeling for Prescription Drugs, Revised Draft Guidance, August 2015, p. 6.

As noted above, disease awareness communications include recommendations or other statements about screening and treatment of a disease or health condition in primary care settings without mentioning a specific drug product.⁹⁸ FDA has said that “disease awareness communications should be designed with certain principles in mind” and that “in general, disease awareness communications should:

- a. be disease- or health condition-specific;
- b. enhance consumer or health care practitioner education;
- c. be clear and accurate;
- d. identify the population at risk or affected by the disease or health condition; and
- e. contain a responsible public health message (i.e., information on the prevention, diagnosis or treatment of a disease or condition).⁹⁹

FDA also has said that disease awareness communications aimed at consumers should “refer consumers to a qualified health care practitioner for more information; and avoid encouraging self-diagnosis and self-treatment.”¹⁰⁰ A disease awareness communication that conveys the message, “There is help for a particular medical condition; see your doctor” is a proper communication.¹⁰¹

The group within FDA that is responsible for reviewing and evaluating promotional materials and for issuing guidance documents describing policies and issues relating to compliance with the FDA prescription drug advertising regulations is the Office of Prescription Drug Promotion (OPDP) (formerly the Division of Drug Marketing, Advertising and Communications (DDMAC)). Promotional materials used in the marketplace by the manufacturer are typically not pre-cleared or approved by FDA,¹⁰² but are to be submitted to DDMAC/OPDP at the time of their dissemination or publication date to facilitate FDA’s oversight of promotional materials.¹⁰³ (For drug products for the treatment of serious or life-threatening illnesses and that provide meaningful benefit to patients over existing treatments that are approved by FDA under the accelerated approval regulations – 21 CFR 314.500 – promotional materials are to be submitted to FDA prior to dissemination for

⁹⁸ Ibid, p. 4.

⁹⁹ Ibid, p. 5.

¹⁰⁰ Ibid.

¹⁰¹ Ibid.

¹⁰² FD&C Act, section 502(n).

¹⁰³ 21 CFR 314.81(b)(3)(i).

FDA's consideration.¹⁰⁴) DDMAC/OPDP is expected to review the promotional materials submitted and advise the pharmaceutical company if the materials violate FDA regulations.¹⁰⁵ If DDMAC/OPDP finds materials that it believes are inconsistent with the product labeling or otherwise violate the prescription drug advertising regulations, it will take enforcement action and issue "Untitled Letters" or "Warning Letters" to the manufacturer requesting revisions, corrections or withdrawals of promotional materials.¹⁰⁶ These FDA enforcement letters reflect DDMAC's interpretation of the promotional materials and how they are believed to violate the advertising and promotion regulations. Thus, these letters typically open with phraseology such as, "These materials violate the Federal Food, Drug, and Cosmetic Act and its implementing regulations," and, "these materials are false and misleading", and "these materials misbrand the product," indicating not that such frank determinations have been established, but that such is DDMAC's belief based upon their interpretation of the promotional materials. FDA also has available other enforcement tools including initiation of misbranding proceedings and product seizure. If DDMAC/OPDP does not take enforcement action, it is reasonable for the manufacturer to understand that DDMAC/OPDP does not object to the promotional materials it has submitted to FDA.

Although not a standard practice, a sponsor may submit new promotional materials to OPDP for review and comment on a voluntary basis so that OPDP may review those materials in conjunction with the FDA-approved product labeling and provide comments back to the sponsor about the acceptability of the materials before the promotional materials are implemented in the marketplace.¹⁰⁷ OPDP's advisory comments are not representative of any type of enforcement action given that the materials are merely drafts that have not been disseminated to the public or healthcare providers.

¹⁰⁴ 21 CFR 314.550.

¹⁰⁵

<https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDE R/ucm090142.htm>.

¹⁰⁶ Ibid.

¹⁰⁷ Guidance for Industry – Providing Regulatory Submissions in Electronic and Non-Electronic Format – Promotional Labeling and Advertising Materials for Human Prescription Drugs, Draft Guidance, April 2015, p. 8.

Competitors of a manufacturer also may submit complaints to FDA about the manufacturer's promotional materials, which may provoke additional review of a manufacturer's promotional materials and possible enforcement actions by FDA.¹⁰⁸ Those kinds of competitor complaints are not uncommon, particularly in the case of multiple manufacturers of products in a therapeutic class. Doctors and other health care professionals and consumers also can submit complaints to DDMAC/OPDP about a manufacturer's promotional materials.¹⁰⁹

It is important to note here that it is paramount to consider the entirety of the promotional piece to evaluate its promotional message both with respect to the risk information in the advertisement and how the information about the indicated use of the product, or efficacy, is characterized throughout the entire promotional piece, not just on one page or even in one heading.¹¹⁰ FDA expanded on this concept in a recent draft guidance, "It is important to emphasize that when FDA evaluates the risk communication in a promotional piece, FDA looks not just at specific risk-related statements, but at the **net impression** i.e., the message communicated by all elements of the piece as a whole. The purpose of the evaluation is to determine whether the piece **as a whole** conveys an accurate and non-misleading impression of the benefits and risks of the promoted product."¹¹¹ The promotional message is, oftentimes, built through the entire piece to fully describe the appropriate uses of the product and the limitations and risks associated with such uses.

B. FDAAA Amendments of 2007

In September 2007 the Federal Food Drug and Cosmetic Act was amended with the Food and Drug Administration Amendments Act (FDAAA) of 2007.¹¹² FDAAA had numerous provisions including reauthorization of User Fees for drugs and medical devices and several

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<https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDE/ucm090142.htm>.

¹⁰⁹ Ibid.

¹¹⁰ 21 CFR 202.1(e)(3).

¹¹¹ Guidance for Industry – Presenting Risk Information in Prescription Drug and Medical Device Promotion, Draft Guidance, May 2009, p. 4.

¹¹²

<https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstotheFDCA/foodanddrugadministrationamendmentsof2007/default.htm>

provisions to facilitate studies of drugs with use in children and to support the development of important new safety, effectiveness and dosing information for drugs used in children.¹¹³ Other provisions addressed food safety, the use of advisory committees, clinical trial registries, and multiple approaches to enhance drug safety.

One particular provision of FDAAA to note in this report is section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act, which was added by section 901 of FDAAA. This section authorizes FDA to require certain drug application holders to make safety-related labeling changes to prescription drug products if FDA becomes aware of new safety information that FDA believes should be included in the labeling of the drug.¹¹⁴ New safety information is defined as information derived from a clinical trial, and adverse event report, a post-approval study, peer-reviewed biomedical literature, data derived from postmarket risk identification and analysis, or other scientific data deemed appropriate by FDA about a serious risk or an unexpected serious risk associated with use of the drug that FDA has become aware of since the drug was approved.¹¹⁵ Prior to FDAAA, if FDA identified important new safety risks it would request that the manufacturer make an appropriate labeling change. In most cases, the sponsor would respond to these requests for labeling changes by negotiating the appropriate labeling language with FDA and then submitting the corresponding labeling supplement for FDA review and approval. FDAAA gives FDA the authority to order a label change in the face of new safety information to expedite such a change if warranted and the corresponding enforcement tools to ensure timely implementation.

C. Labeling Format Change – PLR Labeling (2006)

As noted above, prescription drug labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.¹¹⁶ On January 24, 2006 FDA published an amended regulation on the content and format of prescription drug labeling.¹¹⁷ This revised format and content regulation became known as the Physician

¹¹³ Ibid.

¹¹⁴ Guidance for Industry – Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act, July 2013.

¹¹⁵ Ibid.

¹¹⁶ 21 CFR 314.56(a)(1).

¹¹⁷ 71 FR 3922-3997.

Labeling Rule (PLR).

The new labeling format requires that prescription drug labeling include a Highlights section, a Table of Contents, and a description of Recent Major Changes to the label, and reordered certain labeling sections in an effort to make it easier for prescribers to read and use the labeling information to enhance the safe and effective use of drug products and reduce adverse reactions.¹¹⁸

With respect to clinical safety information in prescription drug labeling, while certain safety information is included in the Highlights section, and the Warnings section and Precautions section in the previous labeling regulation was consolidated into one combined Warnings and Precautions section, the essential content of the safety information in the Contraindications, the Warnings and Precautions, and the Adverse Reactions sections of the prescription drug labeling regulations is little changed from the previous version of the prescription drug labeling content and format implemented in 1979.¹¹⁹ For example, the new PLR regulation retains the same definition of an adverse reaction as before; “(a)n adverse reaction is an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence,” but adds that, “This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.”¹²⁰ Thus, the listing of an adverse reaction for a drug product under this regulation does not establish that a definitive causal relationship between the product and the adverse reaction has been established, only that there is a reasonable association between the two. Similarly, even a drug Warning is to be listed where “there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.”¹²¹ Importantly, FDA “emphasizes that reviewer and applicant **judgment** remain critical in assessing **how** or **whether** to present information on an adverse reaction”¹²² (emphasis added).

¹¹⁸ 71 FR 3922.

¹¹⁹ 44 FR 37434-37467.

¹²⁰ 21 CFR 201.57(b)(7).

¹²¹ 21 CFR 201.57(b)(6).

¹²² Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, January 2006, p. 1.

The PLR labeling regulation describes which types of adverse reactions should be characterized in the Warnings and Precautions section of the labeling, “This section must describe *clinically significant adverse reactions* (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacologic class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification).”¹²³ The FDA Guidance for Labeled Warnings notes that, “The WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or *otherwise clinically significant* because they have implications for prescribing decisions or patient management.”¹²⁴ Adverse reactions that are serious are those that result in death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.¹²⁵ This is, purposefully, a high threshold to consider an adverse reaction to be serious. FDA references the ICH E2A Guideline, “which states that a serious adverse drug experience is based on events that pose a threat to a patient’s life or functioning and not on events of relatively minor medical significance.”¹²⁶ To demonstrate this high threshold, FDA provides an example of a serious adverse drug experience that results in a significant or persistent disability/incapacity as “persons incarcerated because of actions allegedly caused by a drug (e.g., psychotropic drugs and rage reactions) have sustained a substantial disruption in their ability to conduct normal life functions.”¹²⁷ Adverse reactions that are otherwise clinically significant are those that have a “significant impact on clinical use of the drug,” and “those that have significant impact on therapeutic decision-making.”¹²⁸ FDA clarifies that the seriousness of the disease treated and the seriousness of the adverse reaction must both be considered in what is essentially a benefit-

¹²³ 21 CFR 201.57(b)(6).

¹²⁴ Guidance for Industry – Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, October 2011, p. 3.

¹²⁵ 21 CFR 314.80(a).

¹²⁶ 62 FR 52242.

¹²⁷ Guidance for Industry, Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, Draft Guidance, March 2001, p. 7.

¹²⁸ 71 FR 3946.

risk judgment to determine if an adverse reaction is otherwise clinically significant..."The relative seriousness of the disease or condition treated should be considered. For example, non-serious adverse reactions (e.g., nausea, pruritis, alopecia) caused by drugs intended to treat minor, self-limiting conditions (e.g., allergic rhinitis, cosmetic conditions, transient insomnia) may be considered clinically significant. However, those same adverse reactions caused by drugs intended to treat serious or life threatening conditions (e.g., cancer) may be considered much less clinically significant and not appropriate for inclusion in this section,"¹²⁹ (that is, the Warnings section of the label).

It is telling that FDA describes the exact circumstance for Taxotere labeling in its example of not labeling alopecia as a Warning for a drug used to treat cancer where the benefit is survival. This, in my opinion, is true whether the labeling of the adverse reaction is for alopecia, for total or partial alopecia, for persistent or persisting alopecia, for chronic alopecia, ongoing alopecia, long-term alopecia, or for permanent or irreversible alopecia. Hair loss - total, even persistent or irreversible - may very well be a troubling side effect to affected breast cancer patients, but it does not meet the regulatory standards of a serious or otherwise clinically significant adverse drug reaction to constitute a labeled Warning for a product where the corresponding benefit is survival. Describing the risk of alopecia in any form in the labeling of a drug such as Taxotere for the treatment of breast cancer is appropriate in the Adverse Reactions section of the labeling, not in the Warnings section. That has been the judgment of FDA and Sanofi throughout the labeling history of Taxotere, irrespective of how the alopecia was characterized. Importantly, it was also the judgment of the medical reviewers at FDA that labeling for the risk of alopecia with Taxotere was appropriate in the Adverse Reactions section of the label, as will be discussed further in this report. Even when FDA determined in 2015 that the Taxotere labeling should be revised to note that cases of permanent alopecia have been reported, as discussed in Section IV. H. of this report, FDA did not require a labeled Warning, but required additional language to be labeled as a potential Adverse Reaction. Similarly, when the European regulators required that the European SmPC (labeling) be revised to include a potential risk of persistent alopecia, as will be addressed later in this report, even "given the serious psychological consequences of this adverse effect,"¹³⁰ the European Medicines Agency (EMA) and the

¹²⁹ Guidance for Industry – Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, October 2011, p. 4.

¹³⁰ Sanofi_04864365, Sanofi_04864366.

French Health Products Safety Agency (AFSSAPS) required that additional language be added in the Undesirable effects section of the label, not the Special warnings and precautions for use section of the SmPC. (The European Summary of Product Characteristics, the SmPC, is analogous to the US product labeling or package insert. “The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively.”¹³¹ The Undesirable effects section of the SmPC is analogous to the US labeling for Adverse Reactions. “This section (Undesirable effects) should include all adverse reactions from clinical trials, post-authorization safety studies and spontaneous reporting for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.”¹³² That section is contrasted with the SmPC Special warnings and precautions for use section (similar to the US Warnings and precautions section of the label) which includes the “serious adverse reactions to which the healthcare professionals need to be alerted.”¹³³)

Thus, consistent with the FDA and European guidances governing labeling of adverse reactions and warnings, it was the medical judgment of the medical pharmacovigilance and labeling experts at Sanofi, the medical experts at FDA and at EMEA and AFSSAPS that the risk of alopecia, of persisting alopecia, of persistent alopecia or permanent or irreversible alopecia was appropriately labeled for Taxotere in the Adverse Reactions section of the label and that a labeled Warning was not appropriate.

In a similar circumstance, FDA was petitioned to include a labeled boxed warning for risperidone products used for the treatment of significant psychotic disorders, including schizophrenia and bipolar disorder, products known and labeled for the risk of adverse reactions of hyperprolactinemia (elevated prolactin blood levels) and its associated clinical effects, including gynecomastia (breast enlargement)¹³⁴, a condition characterized by the petitioner as chronic and psychologically “devastating” to impacted young male patients.¹³⁵ In its response to the petition, FDA declined to require a boxed warning for risperidone

¹³¹ European Commission, A Guideline on Summary of Product Characteristics (SmPC), September 2009, p. 2.

¹³² Ibid, p. 15.

¹³³ Ibid, p. 11.

¹³⁴ Citizen Petition, FDA-2012-P-0857, Sheller, P.C., August 27, 2012.

¹³⁵ Ibid, p. 14.

products for gynecomastia because “Gynecomastia is a common clinical manifestation of hyperprolactinemia...and does not represent a serious adverse event as defined in 21 CFR 312.23(a).”¹³⁶ Thus, FDA declined to include a labeled warning for a chronic, psychologically devastating adverse reaction since such reaction did not meet the clinical regulatory criteria as a serious adverse event. FDA added that the risk of gynecomastia was “well known” and that “We would expect prescribers and patients to discuss these potential risks (together with the potential benefits) before and during treatment, consistent with the applicable standard of care.”¹³⁷

The FDA’s Guidance for Industry; Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, notes a number of factors to be considered when determining whether there is reasonable evidence of a causal association. These include:

- The frequency of reporting
- Whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials
- Evidence of a dose-response relationship
- The extent to which the adverse event is consistent with the pharmacology of the drug
- The temporal association between drug administration and the event
- Existence of dechallenge and rechallenge experience
- Whether the adverse event is known to be caused by related drugs.¹³⁸

The related FDA Guidance for the Adverse Reactions section of the labeling references the same factors, but only requires that there is some basis to believe there is a causal relationship between the drug and the event. It also states that “[d]ecisions on whether there is some basis to believe there is a causal relationship **are a matter of judgment.**”¹³⁹

¹³⁶ Citizen Petition, FDA-2012-P-0857, FDA response, November 25, 2014, p. 7.

¹³⁷ Ibid, pp 6-7.

¹³⁸ Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, October 2011, p. 3.

¹³⁹ Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, January 2006, p. 8.

Additionally, the FDA Guidance on Good Pharmacovigilance Practices notes factors which may suggest a causal relationship between the use of a product and an adverse event:

- Occurrence of the adverse event in the expected time
- Absence of symptoms related to the event prior to exposure
- Evidence of positive dechallenge or positive rechallenge
- Consistency of the event with the established pharmacological/toxicological effects of the product
- Consistency of the event with the known effects of other products in the class
- Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiological studies
- Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).¹⁴⁰

When determining causal association of an adverse event associated with a product, many factors are evaluated in making a determination as to whether that event is appropriate for the adverse reaction or warning section. That assessment is a complex medical judgment that is undertaken by the medical experts at the sponsoring company and the FDA. There is no formula.

Thus, the multiple FDA guidances for causality assessments describe a complex set of criteria to be considered which will then be evaluated through the medical judgment of the reviewers both at FDA and the sponsor to make a determination if labeling of that event is warranted and how the adverse reaction is to be characterized. Relevant to this report, alopecia during chemotherapy is known and expected. For this reason, from the initial approval of Taxotere, and throughout its time on the market, alopecia has been labeled for Taxotere. How information about alopecia was developed and how the labeling characterized alopecia over time is described throughout this report.

Returning to the PLR content and format regulation, it requires that the adverse reactions “must be categorized by body system, by severity of the reaction, or in order of decreasing

¹⁴⁰ Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, March 2005, pp. 6-7.

frequency, or by a combination of these, as appropriate.”¹⁴¹ In practice, the frequency of occurrence of adverse reactions in the clinical trials has become the predominant aspect of characterizing and presenting adverse reactions in labeling. The regulation¹⁴² calls for a listing of adverse reactions that occurred at or above a specified rate appropriate to the safety database and that the rate of adverse reactions seen with active or placebo comparators also be presented. This section of the regulation also contemplates listing of certain adverse reactions that occurred in a frequency below the specified rate, but that they would be reported in a separate listing. The regulation further notes the need to include adverse reactions reported in postmarketing experience¹⁴³, but these are listed in practice just as a reflection of their occurrence, not their frequency (due to the limitations of postmarketing surveillance data in determining frequency of events as described above).

The characterization of safety information in the labeling is, as noted above, a summary of the essential information to allow for the safe use of the drug. There is not a simple, formulaic approach to determine such labeling. Prescription drug labeling instead reflects the complex, collaborative medical judgment of both the FDA and the sponsor. For example, in one of FDA’s accompanying labeling guidance documents, the Agency notes “reviewer and applicant judgment remain critical in assessing how or whether to present information on an adverse reaction.”¹⁴⁴ However, the FDA remains the ultimate arbiter. This is clearly described in the preamble to the PLR labeling rule, “Under the Act, FDA is the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective, and that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading,” and “In fact, the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA’s under the act.”¹⁴⁵

The safety information in the FDA-approved labeling reflects the FDA’s assessment and evaluation of the sponsor’s submitted clinical data, of the sponsor’s evaluation of those data, of the determination of the frequency of the occurrence of the adverse reactions (not the establishment of a definitive causality), and of the sponsor’s proposed labeling. In the

¹⁴¹ 21 CFR 201.57(b)(7)(ii).

¹⁴² 21 CFR 201.57(b)(7)(ii)(A).

¹⁴³ 21 CFR 201.57(b)(7)(ii)(B).

¹⁴⁴ Guidance for Industry – Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, January 2006, p. 1.

¹⁴⁵ 71 FR 3934.

course of that assessment and evaluation by FDA there is dialog and a sharing of opinions between the sponsor and FDA in what can be considered a collaborative process. But, at the end of the process, FDA has the ultimate authority and makes the ultimate decision on what is in the FDA-approved labeling.

D. Other Labeling Conventions

1. Summary of Product Characteristics (SmPC)

In the European regulatory environment, approved prescription drug labeling is included in the Summary of Product Characteristics or SmPC. “The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively.”¹⁴⁶ The SmPC has labeling sections similar to that called for in the US product label:

1. Name of Medicinal Product
2. Qualitative and Quantitative Composition
3. Pharmaceutical Form
4. Clinical Particulars
 - 4.1. Therapeutic indications
 - 4.2. Posology (dosing) and method of administration
 - 4.3. Contraindications
 - 4.4. Special warnings and precautions for use
 - 4.5. Interaction with other medicinal products and other forms of interaction
 - 4.6. Fertility, pregnancy and lactation
 - 4.7. Effects on ability to drive and use machines
 - 4.8. Undesirable effects
 - 4.9. Overdose
5. Pharmacological Properties
 - 5.1 Pharmacodynamic properties
 - 5.2 Pharmacokinetic properties
 - 5.3 Preclinical safety data
6. Pharmaceutical Particulars

¹⁴⁶ European Commission, A Guideline on Summary of Product Characteristics (SmPC), September 2009, p. 2.

- 6.1 List of excipients
- 6.2 Incompatibilities
- 6.3 Shelf life
- 6.4 Special precaution for storage
- 6.5 Nature and contents of container
- 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
- 7. Marketing Authorization Holder
- 8. Marketing Authorization Number
- 9. Date of First Authorization/Renewal of the Authorization
- 10. Date of Revision of the Text¹⁴⁷

2. Company Core Data Sheet (CCDS), Company Core Safety Information (CCSI)

As described above, the Company Core Safety Information and the Company Core Data Sheet are internal documents, not true labeling, that serve as a foundation for discussions with local regulatory authorities to develop approved product labeling for that region. These documents also serve as a basis in postmarketing pharmacovigilance to determine the “expectedness” of reported adverse events.

The Company Core Safety Information (CCSI) is to reflect the cumulative knowledge regarding the safety of the product and is to contain a defined set of safety data and advice that the company intends to have reflected in the national labeling worldwide, except where the local regulatory authority requires a modification.^{148,149} The CCSI is not negotiated

¹⁴⁷ European Commission, A Guideline on Summary of Product Characteristics (SmPC), September 2009.

¹⁴⁸ International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Periodic Benefit-Risk Evaluation Report (PBRER), E2C(R2), December 17, 2012, p. 26.

¹⁴⁹ MedDRA and Product Labeling: “Best Practices” Recommendations, MSSO-DI-8381-3.0.0, April 15, 2005, p. 2

between the sponsor and the regulatory authorities.¹⁵⁰ Thus, the CCSI serves as an internal foundation or basis for safety-related labeling discussions between the local affiliates of the sponsor company and the local regulatory authority.¹⁵¹ But, the local national regulatory agency retains the authority to determine the ultimate content of the local label. Thus, “Compared to the CCSI, the national/regional HP labeling may contain more, less or different safety information.”¹⁵²

The pharmacovigilance environment has evolved such that the regulatory authorities have recognized that the assessment of risks of drug products is most meaningful when considered in light of its benefits.¹⁵³ To allow for the inclusion of benefits in the supporting reference document, the CCSI or reference safety information concept has been expanded to include the approved indications for the product in the three ICH regions and information on dosing, pharmacology and other issues beyond the core safety information in the Company Core Data Sheet (CCDS).¹⁵⁴

Sanofi included in its PSURs for docetaxel as the PSUR-required Company Reference Safety Information, the Sanofi Company Core Safety Information including all the mandatory and non-mandatory safety information but also additional information such as the indications, dosing, pharmacokinetics and pharmacodynamics and information about the physical properties of the drug itself. [See for example Docetaxel Company Core Safety Information, Version 24, December 14, 2009.¹⁵⁵] Sanofi prepared more comprehensive internal Docetaxel Core Data Sheets that were not provided to the regulatory authorities in the pharmacovigilance process. These CCDSs contained all the core safety information contained in the docetaxel CCSIs, both mandatory and non-mandatory, but the CCDSs further served as an internal reference for the company affiliates in that they also included additional information on the product preparation, storage and handling, container-closure systems, pharmacokinetics and pharmacodynamics, and provided significant more detail on docetaxel clinical studies, principally related to efficacy analyses, since the full safety

¹⁵⁰ Ibid.

¹⁵¹ Ibid.

¹⁵² Ibid.

¹⁵³ International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Periodic Benefit-Risk Evaluation Report (PBRER), E2C(R2), December 17, 2012, p. 1.

¹⁵⁴ Ibid.

¹⁵⁵ Sanofi_02400213.

information was already fully presented in the CCSIs. The specific content of the Sanofi docetaxel CCSI and CCDS documents is described later in this report.

IV. Approval, Postmarketing Surveillance, and Advertising and Labeling History of Taxotere

A. Initial NDA Approval and Labeling

The Taxotere NDA, NDA 20-449, was submitted to FDA on July 27, 1994 by Rhone Poulenc Rorer (RPR) (Rhone Poulenc Rorer merged with Hoechst Marion Roussel in 1999 to form Aventis, Aventis merged with Sanofi Synthelabo in 2004 to form sanofi-aventis = Sanofi) for the proposed treatment of “patients with locally advanced or metastatic breast carcinoma in whom previous therapy has failed; prior therapy should have included an anthracycline unless clinically contraindicated.”¹⁵⁶ (The initial NDA also proposed an indication for the treatment of “patients with locally advanced or metastatic non-small cell lung cancer even after failure of platinum-based chemotherapy.” This report will focus solely on the breast cancer indications for Taxotere and will not address other possible uses of the product.)

The NDA was reviewed for clinical safety and efficacy in the Division of Oncology and Pulmonary Drug Products by the Medical Officer, Dr. Julie Beitz, and other reviewers including Division Director, Dr. Robert Justice.¹⁵⁷ The NDA application was also considered by the FDA Oncologic Drugs Advisory Committee twice before approval: on December 13, 1994 and later on October 17, 1995. The NDA was originally approved on May 14, 1996 for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.¹⁵⁸

During the review of the NDA by FDA, the safety profile of Taxotere was considered thoroughly, including the risk of alopecia.¹⁵⁹ The risk of alopecia associated with Taxotere was also presented to the 1994 and 1995 ODAC meetings as part of the presentation of the

¹⁵⁶ Sanofi_00654954, at Sanofi_00654999.

¹⁵⁷ Ibid.

¹⁵⁸ Sanofi_01380011-15.

¹⁵⁹ Sanofi_00654954, at Sanofi_00655002 and Sanofi_00655011.

safety profile of the product.^{160,161} Concerns were raised by the FDA reviewers and the 1994 ODAC committee members about the approvability of Taxotere, including concerns about its safety profile and how it compared to the safety profile of Taxol; however, those concerns did not include the risk of alopecia, let alone persistent alopecia. The concerns were characterized as: toxic deaths, febrile neutropenia and infection, fluid retention, performance status of patients included in Taxotere clinical trials, and multicenter nature of Taxotere clinical trials.¹⁶² After Rhone Poulenc Rorer addressed the concerns of the FDA reviewers and those of the 1994 ODAC through the submission of additional data, analyses and other clarifying information, ODAC supported approval, FDA found the NDA approvable¹⁶³ and the NDA was approved under FDA's provisions for accelerated approval which address drug products for serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments¹⁶⁴ on May 14, 1996.¹⁶⁵ (Sanofi subsequently submitted the required clinical data to verify the clinical benefit of Taxotere in the treatment of locally advanced or metastatic breast cancer to FDA on December 22, 1997 and FDA noted the fulfillment of the post-approval commitment and removal of the accelerated approval conditions in a June 22, 1998 letter.¹⁶⁶)

The initial labeling approved on May 14, 1996 included information about the risk of alopecia with its listing in the Adverse Reactions section of the label in a tabular listing of adverse events. As described above, the Adverse Reactions section was and is an appropriate section of the labeling to advise of the risk of alopecia. Alopecia is an adverse reaction as defined in the labeling regulations, "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence."¹⁶⁷ This Adverse Reaction labeling provides "information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients."¹⁶⁸ The labeling advises of the risk of alopecia as an

¹⁶⁰ Sanofi_001317, at Sanofi_001358.

¹⁶¹ Rhone Poulenc Rorer, Taxotere Specific Safety Analysis, March 9, 1995, Appendix V, p. 3.

¹⁶² Ibid, p. 3.

¹⁶³ Sanofi_01866065.

¹⁶⁴ 21 CFR 314.500, 21 CFR 314.510.

¹⁶⁵ Sanofi_01380011-15.

¹⁶⁶ NDA 20-449/S-005 approval letter, Temple to Martin, June 22, 1998.

¹⁶⁷ 21 CFR 201.57(c)(7).

¹⁶⁸ Guidance for Industry – Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, January 2006, p. 2.

adverse reaction associated with Taxotere. It does not limit that advice to whether alopecia might be partial or total, mild or severe, the timing of its onset or whether it be temporary, chronic or permanent. This was explained by the Sanofi Global Safety Officer Dr. Emanuel Palatinsky, “Q- Alopecia, the word ‘alopecia’ accounts for irreversible alopecia? A – It includes also irreversible,”¹⁶⁹ and “A – They were warned about persistent alopecia because the concept of persistent alopecia is inherent to alopecia. A physician reading the USPI and a patient reading the patient – the product information leaflet will know that alopecia is reversible or it might not be reversible.”¹⁷⁰

Moreover, alopecia means “hair loss.” There is no consensus definition for “ongoing,” “persistent,” “permanent,” or “irreversible” alopecia. The Medical Dictionary for Regulatory Activities (MedDRA), for example, is the single standardized international medical terminology that can be used for regulatory communication and evaluation.¹⁷¹ FDA has mandated that companies code adverse events observed in clinical trials in accordance with the MedDRA dictionary.¹⁷² Further, FDA uses MedDRA terminology for all adverse event reporting in the FAERS database.¹⁷³ MedDRA contains an entry for the term “Alopecia.” It does not, however, recognize entries for “ongoing,” “persistent,” “permanent,” or “irreversible” alopecia. Accordingly, Sanofi’s use of the term “alopecia” in its physician labeling appropriately characterized the risk of hair loss with the use of docetaxel.

As described above, the labeling of alopecia as an Adverse Reaction and not a Warning is appropriate in that the occurrence of alopecia, even permanent alopecia, would not meet the regulatory criteria of a serious or otherwise clinically significant adverse event; criteria

¹⁶⁹ Palatinsky deposition, August 9, 2018, p. 220.

¹⁷⁰ Palatinsky deposition, August 10, 2018, p. 432.

¹⁷¹ *Vision for MedDra*, MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES, <https://www.meddra.org/about-meddra/vision> (last visited November 12, 2018).

¹⁷² Electronic Study Data Submission; Data Standards; Support for Version Update of the Medical Dictionary for Regulatory Activities, 82 FR 41416, 41416 – 41417 (August 31, 2017).

¹⁷³ *Questions and Answers on FDA’s Adverse Event Reporting System (FAERS)*, U.S. FOOD AND DRUG ADMIN., <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> (last updated June 4, 2018).

to be met to be listed in the Warnings and Precautions section of drug labeling.¹⁷⁴ Adverse reactions are serious if they result in death, are life-threatening, require in-patient hospitalization or prolongation of an in-patient hospitalization, create a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or are a congenital anomaly or birth defect.¹⁷⁵ “Adverse reactions that are otherwise clinically significant include those that may lead to a potentially serious outcome unless the dosage or regimen is adjusted, the drug is discontinued, or another drug is administered to prevent the serious outcome; those that could be prevented or managed with appropriate patient selection, monitoring, or avoidance of concomitant therapy, and prevention or management of the adverse reaction is needed to avoid a potentially serious outcome; and those that can significantly affect patient compliance, particularly when noncompliance has potentially serious consequences.”¹⁷⁶ Even when FDA requested an update to the Taxotere label to describe reports of permanent alopecia in 2015, as described later in this report, it required that such risk information be included in the Adverse Reactions and Patient Labeling sections, not the Warnings and Precautions section of the label.¹⁷⁷ Thus, it is my opinion that alopecia was reasonably and appropriately labeled as an Adverse Reaction for Taxotere in the treatment of metastatic breast cancer.

Furthermore, in the initial Taxotere patient labeling approved on May 14, 1996, it is noted, “*What are the possible side effects of Taxotere?* **Hair Loss** – Loss of hair occurs in most patients taking Taxotere (including the hair on your head, underarm hair, pubic hair, eyebrows and eyelashes). Hair loss will begin after the first few treatments and varies from patient to patient. Once you have completed all your treatments, hair generally grows back.”¹⁷⁸ Here the patient is advised that hair loss occurs in most patients, is significant-to-total, persists through the duration of treatment, and may be permanent as it is noted that even after discontinuation of therapy, hair generally (not always) grows back. This was also clarified by Dr. Palatinsky, “It doesn’t say ‘will return,’” and “It says ‘Hair growth should

¹⁷⁴ Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, October 2011, p. 3.

¹⁷⁵ Ibid.

¹⁷⁶ Ibid, p. 4.

¹⁷⁷ Sanofi_00805353.

¹⁷⁸ Sanofi_000001, at Sanofi_000003.

occur'...which means it may or may not."¹⁷⁹ Dr. Palatinsky added, "That's an important statement. It tells the reader that after treatment, the hair growth should return to normal. But it might not necessarily return to normal," and "It tells me that this document is communicating to the reader that in a majority of patients, the hair loss will recover, and in a minority of patients, it may not."¹⁸⁰

This characterization of hair loss associated with chemotherapy agents ("hair generally grows back"), such as with Taxotere, was widely employed by FDA, essentially as class labeling for oncology products. As described in section IV. E. of this report, the labeling for Taxol, a product also with reports of irreversible hair loss¹⁸¹, noted that "Hair generally grows back after you've finished your Taxol treatment."¹⁸² Similarly, the labeling for Abraxane, another paclitaxel formulation, noted that "Hair generally grows back after you've finished your Abraxane treatment."¹⁸³ Also, the labeling for doxorubicin noted the potential for hair loss, but added, "your hair may re-grow after your treatment."¹⁸⁴ Accordingly, such labeling about the potential regrowth of hair after treatment with such cytotoxic agents was/is not considered by FDA to be misleading.

Thus, the initial FDA-approved labeling for Taxotere advised both healthcare providers and patients of the risk of hair loss or alopecia. The labeling advice for the risk of alopecia has remained in the Taxotere labeling through to the current time. The variations of this advice of risk of alopecia through time are described later in this report.

The FDA review of Taxotere was comprehensive, employing multiple review disciplines including Chemistry, Pharmacology, Biopharmaceutics, Statistics and most relevant to this report, the Medical review of both safety and efficacy. There were multiple Medical reviews that lead to the FDA decision to approve Taxotere, which were verified and confirmed by the Division Director. These reviews were supplemented by two reviews by the ODAC. The reviews were thorough and detailed with the total time from NDA submission to FDA approval taking nearly two years.

¹⁷⁹ Palatinsky deposition, August 9, 2018, pp. 163-64.

¹⁸⁰ Palatinsky deposition, August 10, 2018, pp. 497, 501.

¹⁸¹ Prevezas, c., et. al., Irreversible and severe alopecia following docetaxel or paclitaxel cytotoxic therapy for breast cancer. Br. J. Dermatol. 160(4):883-885.

¹⁸² NDA 20-262, Labeling Review, March 4, 2002.

¹⁸³ NDA 21-660, S-022, approved June 26, 2009.

¹⁸⁴ NDA 50-629, S-019, approved September 26, 2011.

The FDA and ODAC reviewed the data and analyses presented by Rhone Poulenc Rorer in their evaluation of the safety and efficacy of Taxotere in metastatic breast cancer, but also relied upon their experience in reviewing other cancer drugs in general and agents for the treatment of metastatic breast cancer specifically; most importantly, Taxol which had been approved just two years earlier.¹⁸⁵ The determination was made that the benefit/risk of Taxotere for metastatic breast cancer was positive; the benefits outweighed the potential risks and the labeling provided adequate directions for the safe use of the product for its intended uses. That determination was first made for Taxotere in the May 14, 1996 initial approval and was reaffirmed time and again as FDA reviewed and approved revised labeling for Taxotere with each labeling supplement (see below) attesting to the adequacy of that labeling to allow for the continued safe and effective use of Taxotere.

It is my opinion that the decision on the part of FDA to approve and label Taxotere for the treatment of metastatic breast cancer was reasonable and appropriate from a regulatory perspective given the solid anti-tumor efficacy consistently demonstrated by Taxotere in clinical trials and the safety profile in metastatic breast cancer patients which was shown to be similar to that of other agents in the field, agents that were well-studied, familiar to FDA and ODAC, and already subject to significant use in the market in a large treatment population.

B. TAX316 – Taxotere in Combination with Doxorubicin and Cyclophosphamide for the Adjuvant Treatment of Patients with Operable Node-Positive Breast Cancer

On March 17, 2004, Sanofi submitted Taxotere supplemental NDA S-029 to FDA to provide for Taxotere to be used in combination with doxorubicin and cyclophosphamide for the treatment of patients with operable node-positive breast cancer (node positive breast cancer). Included in that submission was Clinical Study Report RP56976V – 316, “A Multicenter Phase III Randomized Trial Comparing Docetaxel in Combination with Doxorubicin and Cyclophosphamide (TAC) versus 5-Fluorouracil in Combination with Doxorubicin and Cyclophosphamide (FAC) as Adjuvant Treatment of Operable Breast

¹⁸⁵ NDA 20-262, approved December 29, 1992.

Cancer Patients with Positive Axillary Lymph Nodes,” (TAX316). The report presented results of the second interim analysis of this study with 55 months median patient post-treatment follow-up. Unlike earlier clinical studies with Taxotere in the treatment of metastatic breast cancer in patients having failed prior chemotherapy, this study allowed for significant post-therapy follow-up of the patients because of the good post-therapy prognosis in this population. The study was designed for patients to be treated with six cycles of therapy and then followed for up to 10 years post-treatment. Thus, the study design allowed for the analysis of long term-safety of those adverse events persisting into this follow-up period. This was possible because the 5-year overall survival of the TAC treated patients was 87%.¹⁸⁶ This is in contrast to the Taxotere previously-treated metastatic breast cancer trials in the original NDA where the survival of patients was much shorter, generally ranging about one year in duration.¹⁸⁷ The TAX316 clinical study report (CSR) from the second interim analysis at 55 months median follow-up noted in its analysis of “persistent adverse reactions” that 3.2% of the TAC treated patients showed alopecia ongoing into the follow-up period.¹⁸⁸ This finding was presented in both text and tabular displays in the Study Synopsis, Safety Results, Safety Summary and Discussion sections of the CSR.¹⁸⁹

To provide some context to this finding, the 3.2% of TAC treated patients with alopecia still ongoing into the follow-up period represented 22 of the 687 TAC treated patients who demonstrated alopecia at the start of the follow-up period from among the 744 patients in the TAC-treated group overall.¹⁹⁰ This does not represent a frequency of “persistent alopecia,”¹⁹¹ let alone a frequency of permanent or irreversible alopecia. In his October 11, 2018 deposition, Michael Kopreski, M.D., an oncologist and former pharmacovigilance officer at Sanofi, testified that upon conducting a thorough re-evaluation of the information from each of the patients recorded as presenting ongoing alopecia, he instead found a 0.9% frequency of persistent alopecia in the TAC group from the TAX316 study at the 55-month

¹⁸⁶ Sanofi_00355622.

¹⁸⁷ Sanofi_00655001.

¹⁸⁸ Sanofi_00798650.

¹⁸⁹ Ibid.

¹⁹⁰ Ibid.

¹⁹¹ It is my understanding that the Court defined “persistent alopecia” for purposes of the Kopreski depositions as alopecia “that which remains six months after chemotherapy ended without resolution.”

follow-up point.¹⁹² Dr. Kopreski arrived at this frequency of persistent alopecia of less than 1%, or 7 patients of the 744 patients in the TAC group, through his review of the individual patient data to ensure that the patient met the criteria of persistent alopecia, that is alopecia that was documented to be present at least six months after the last dose of chemotherapy and where there was no documentation of subsequent resolution in the follow-up period.¹⁹³ That is, there needed to be documented evidence of the ongoing nature of the alopecia (absence of evidence of ongoing nature is not evidence of persistence) at least six months following the completion of therapy and evidence that it the alopecia is related to docetaxel therapy to be considered a report of persistent alopecia. Through the same approach, Dr. Kopreski determined a frequency of persistent alopecia in the FAC arm in TAX316 at the 55-month follow-up point of 0.4%.

The TAX316 study represents the best source of information on the frequency of persistent alopecia associated with Taxotere therapy. It was a large controlled clinical study with a population of nearly 1500 patients enrolled, followed for a period of up to 10 years.¹⁹⁴ Dr. Kopreski characterized the TAX316 study as “a very well designed and controlled study. And part of the endpoints of the study was to look at the long-term assessment...of safety, of safety issues, including alopecia.”¹⁹⁵ FDA notes that estimations of the frequency of adverse reactions best come from “adequate and well-controlled clinical studies,”¹⁹⁶ and not from postmarketing experience with the drug.¹⁹⁷ Published case reports and studies involving smaller groupings of patients will not be as robust as a large, controlled clinical study such as TAX316 and, consequently, adverse reaction frequency estimates will not be feasible or

¹⁹² Kopreski deposition, October 11, 2018, p. 728.

¹⁹³ Ibid, p. 729.

¹⁹⁴ Sanofi_01288423.

¹⁹⁵ Kopreski deposition, October 11, 2018, pp. 727-728.

¹⁹⁶ 44 FR 3746; 71 FR 3951, “precise percent figures would be appropriate if there is scientific evidence from well-controlled trials substantiating such figures,”; and Guidance, Classifying Significant Postmarketing Drug Safety Issues, Draft Guidance March 2012, p. 6, “When CDER staff identify a new safety issue, unless the information is derived from a clinical trial or pharmacoepidemiology study, precise and reliable information may be lacking about the frequency of the adverse event,”

¹⁹⁷ 71 FR 3950, “postmarketing experience, although more closely reflective of clinical practice, lacks the structure of a clinical trial setting that permits increase precision. For postmarketing reporting...the frequency with which a suspected adverse reaction is reported and the number of exposures to the drug, compared to the number of suspected reactions reported are unknown, making estimation of incidence calculations difficult.”

will be less reliable. For comparisons of adverse reactions between drugs, “any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity or character of adverse reactions must be based on adequate and well-controlled studies.”¹⁹⁸

This determination (less than 1% persistent alopecia) represents the best estimate of the frequency of persistent alopecia seen in patients receiving the TAC combination regimen from the most robust source of information to make such a determination; better than estimates derived from postmarketing spontaneous reports and published reports of case reports and smaller clinical studies. And, the relevant TAC vs FAC comparison for the frequency of persistent alopecia from this study at 55 months of follow-up is 0.9% vs 0.4%, a relatively small difference. To state that the frequency of irreversible alopecia seen with the TAC group in TAX316 at the 55-month follow-up is 3.2%, as does Dr. Kessler,¹⁹⁹ is inaccurate, false and misleading. The 3.2% frequency is the frequency of ongoing alopecia. Dr. Kopreski calculates a frequency of persistent alopecia of less than 1%. Even a frequency of persistent alopecia provides an over-estimate of the frequency of irreversible alopecia as will be described later in this report at section IV. D. as Sanofi identified cases of persistent alopecia (determined using an even more conservative definition than employed by Dr. Kopreski – persisting for 12-months post-therapy as opposed to 6 months post-therapy) that nonetheless subsequently resolved.²⁰⁰ (Later, Sanofi identified cases of alopecia persisting even more than 2 years after the completion of therapy that subsequently resolved,²⁰¹ questioning whether even 2 years is an adequate cut-off threshold of persistence to qualify such a report as “irreversible”, let alone a threshold of 6-month persistence.) Thus, such cases of persistent alopecia are not cases of truly irreversible alopecia and any calculated frequency of irreversible alopecia determined from such true cases of irreversible alopecia will be less than the frequency of persistent alopecia.

Similarly, when evaluating spontaneous reports of adverse reactions of alopecia, an appropriately robust set of criteria must be established to identify those reports which are truly “irreversible.” Dr. Madigan identified reports from the FAERs database with the adverse reaction term of alopecia and any report tagged with the outcome of “Disability or

¹⁹⁸ 21 CFR 201.57(c)(7)(iii).

¹⁹⁹ See Kessler expert report, paragraphs 96.2, 123.

²⁰⁰ Sanofi_00201089.

²⁰¹ Sanofi_01259408 at p. 6.

Permanent Damage” as reports of “irreversible” alopecia. No consideration of duration, persistence, chronicity or outcome of the report of alopecia was undertaken. Alopecia that was short term or subsequently resolved might still be marked with an outcome of a “Disability” by the reporter (healthcare professional or patient) because of the impact of the adverse reaction on the patient, irrespective of the regulatory definition of such terms. Additionally, alopecia may have been reported as part of a group of adverse events. Therefore the “Disability or Permanent Damage” tag in the FAERS database may apply to a different adverse event reported concomitantly with alopecia. Thus, such a catchment of reports may include reports of alopecia that are not truly irreversible and, thus, related conclusions about frequency or signal detection from such reports may be inflated and biased. This point, that the definition of irreversible alopecia needs to represent a high threshold and not include alopecia events that will subsequently resolve and thus not be truly irreversible, is further reflected in the analysis by Dr. Madigan where nearly 10% of the reported cases identified as “irreversible” alopecia were subsequently resolved.²⁰² Similarly, analyses of internal safety databases, such as Sanofi’s global pharmacovigilance database, to identify reports of “irreversible” alopecia also need to employ rigorous criteria that include an assessment of the timeframe of the alopecia to determine, as was done by Sanofi in 2011 and 2015 as will be discussed below, if such reports are to accurately represent ongoing, or persistent or irreversible alopecia.

Thus, in light of Dr. Kopreski’s calculation of a frequency of persistent alopecia in the TAC group in TAX316 of less than 1%, the 3.2% rate of ongoing alopecia from the 55-month interim analysis of TAX316 in TAC-treated patients, as reported, represents an overestimate of the actual frequency of persistent alopecia found in this study. Dr. Kopreski stated that much of the persistent alopecia seen with the TAC group from TAX316 might be a contribution from the adriamycin and cyclophosphamide (AC) components of the TAC therapy, and not from Taxotere.²⁰³ Thus, the frequency of ongoing alopecia seen with the TAC group from TAX316 at 55 months of follow-up of 3.2% is an inappropriate, inflated figure for the frequency of persistent alopecia, let alone for the frequency or irreversible alopecia.

²⁰² Madigan expert report at paragraph 43.

²⁰³ Kopreski Deposition, October 11, 2018, p. 764.

Sanofi completed a 10-year follow-up for the TAX316 study as will be described below. The TAX316 10-year follow-up analysis showed that 4.2% of the TAC-treated patients demonstrated alopecia that remained ongoing in the follow-up period.²⁰⁴ This report also noted that 2.5% of the FAC-treated patients demonstrated alopecia that remained ongoing in the follow-up period.²⁰⁵ Dr. Kopreski completed a thorough re-evaluation of the individual patient data for the TAX316 10-year follow-up and employed the same criteria as described above for the 55-month interim follow-up (alopecia documented to be present at least 6 months after the completion of chemotherapy and where there was no documentation of subsequent resolution in the follow-up period). Through this analytical approach, testifying on behalf of Sanofi as its corporate representative, Dr. Kopreski determined a frequency of persistent alopecia in the TAC group at the 10-year follow-up of 0.8% (6/744), or again, less than 1%.²⁰⁶ Dr. Kopreski determined a frequency of persistent alopecia in the FAC-treated group at the 10-year follow-up of 0.4% (3/736).²⁰⁷ Thus, this confirms that the best estimate for the frequency of persistent alopecia in the TAC group for the TAX316 study is less than 1%.

With this March 17, 2004 supplemental NDA submission, Sanofi proposed revisions to the Taxotere label to reflect this new proposed indication for adjuvant therapy and other information from the clinical study. Specifically, in addition to another tabular listing of alopecia in the Adverse Reactions section of the labeling, Sanofi proposed to add to the Adverse Reactions section of the label (not the Warnings section, see above) information about adverse reactions that persisted into the follow-up period of the study. Sanofi's labeling proposal for the Adverse Reactions section of the label was to add a subsection, **"Other persistent reactions...**The following events were observed to be ongoing in TAC-treated patients at the median follow-up time of 55 months; alopecia (22/687), amenorrhea (133/233), neurosensory (9/73) and peripheral edema ((18/112)..."²⁰⁸ (The patient labeling information about the risk of hair loss as described above was to be retained as is.) This labeling proposal was resubmitted to FDA on June 23, 2004 in response to an FDA request. Once again, RPR resubmitted this labeling proposal on August 5, 2004 and again

²⁰⁴ Sanofi_00724262, p. 37.

²⁰⁵ Ibid.

²⁰⁶ Kopreski Deposition (Rough Transcript), December 13, 2018, p. 148.

²⁰⁷ Kopreski Deposition (Rough Transcript), December 13, 2018, p. 148.

²⁰⁸ Sanofi_00355202, p. 30.

on August 9, 2004 in response to additional FDA requests.²⁰⁹

After a thorough review by FDA of the submission, reflected in an extensive series of communications between FDA and RPR, principally related to evaluation of individual patients in the study, FDA sent their comments on the proposed labeling to RPR on August 11, 2004.²¹⁰ In those comments, FDA deleted RPR's proposal to add information to the Adverse Reactions section of the Taxotere label information about "Other persistent reactions", including alopecia.²¹¹ It was FDA's deletion of Sanofi's proposed labeling as evidenced by the Track Changes format in Sanofi_04539472.doc, which attributes the deletion to FDA's Ann Staten.²¹² In FDA's appended statement of "reasoning for the FDA's changes to the TAXOTERE label," no basis for the deletion of the Other persistent reactions labeling was provided. FDA provided updated revisions to RPR on August 12, 2004, still proposing to delete the Other persistent reactions labeling.²¹³ After several additional exchanges between RPR and FDA, FDA retained its position with respect to deleting the proposed labeling of Other persistent reactions and approved the supplemental NDA on August 18, 2004, granting the indication for Taxotere in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer without RPR's proposal to include Other persistent reactions, including a description of persisting alopecia, in the Adverse Reactions section of the label.²¹⁴ The patient labeling description of the risk of hair loss remained unchanged from that described above.

Thus, in this supplemental NDA submission, RPR provided clear analysis of the clinical data, describing the persistence of alopecia into the follow-up period after conclusion of treatment of patients with Taxotere. Additionally, RPR proposed on several occasions to include in the Taxotere label information about persistent alopecia in the Adverse Reactions section of the label. Despite these analyses and labeling proposals, FDA approved Taxotere for this node positive breast cancer use, did not require revised labeling for persistent or irreversible alopecia in the Adverse Reactions section of the label, confirmed the adequacy

²⁰⁹ Sanofi_00354861; Sanofi_04817146.

²¹⁰ Sanofi_04817139.

²¹¹ Sanofi_04539472.doc.

²¹² Ibid.

²¹³ Sanofi_00548387.

²¹⁴ Sanofi_04539390.

of the Taxotere labeling to describe the adverse reaction as alopecia without further qualification, did not propose a labeled Warning for persistent or irreversible alopecia and, in fact, specifically deleted Sanofi's proposal for Adverse Reactions labeling of persistent alopecia.

Later, on September 24, 2010 Sanofi-aventis submitted an updated clinical study report for TAX316 containing 10-year follow-up data to fulfill a post-marketing commitment to FDA.²¹⁵ Prior to this submission, in September 2009 a determination was made by Sanofi Regulatory, Statistics and Project Direction that the filing would not include a proposal for revised labeling from Sanofi.²¹⁶ Sanofi's Dr. Gustavson explained the rationale in her deposition, "In this case, the amount of information getting - - provided in the CSR did not warrant a label update,"²¹⁷ and, "I think that the reason that the labeling change was not warranted is it was not deemed to - - needed to be helpful as prescribing information."²¹⁸ Sanofi's Clinical Development and Medical Affairs office, Dr. Barrett Childs further explained, "We had included that information in our label change request with the five-year data. The FDA did not feel that needed to be included in the product label. So the FDA struck that from the revised product label. So we assumed that it was not - if the five-year data was not - if the five-year data was not that important, than the ten-year data would not be that important,"²¹⁹ and "And the data at the five-year follow-up was available at that time. And when we negotiated the label with FDA, and they did not feel that it was important to include that...There would have been no reason to expect that the FDA would have wanted them to revise the label."²²⁰ (As noted above, Dr. Kopreski determined that the frequency of persistent alopecia in the TAC group in this study was less than 1%). This determination was reflected in the conclusion of the clinical study report for the 10-year follow-up to TAX316, "The safety profile of TAC was manageable and consistent with the known toxicity of the individual drugs and of the TAC regimen."²²¹ The TAX316 10 year follow-up analysis showed 4.2% of the TAC treated patients demonstrated alopecia that

²¹⁵ Sanofi_01288423.

²¹⁶ Gustavson Deposition, May 3, 2018, pp. 215-265 and Exhibit 12.

²¹⁷ Gustavson Deposition, May 3, 2018, p. 246,

²¹⁸ Ibid, p. 247.

²¹⁹ Childs deposition, October 26, 2018, pp. 318-319.

²²⁰ Ibid, p. 330.

²²¹ Sanofi_00724262, pp. 5, 71.

remained ongoing in the follow-up period.²²² This is another example of Sanofi clearly sharing data with FDA about persistent alopecia seen in patients treated with Taxotere alongside other chemotherapy agents. On September 23, 2011, FDA responded that it had reviewed the submission of the TAX316 final report with 10 year follow-up data, that the report fulfilled Sanofi's postmarketing commitment, and did not request any change to the Taxotere labeling as a result of its review of the report.²²³

Subsequently, after the Taxotere US label had been revised to reflect the potential risk of permanent alopecia in 2015 (see section IV, H of this report, below), on May 28, 2017 Sanofi submitted a supplemental NDA to, among other changes, update the Taxotere label to add the information from the 10-year follow-up to TAX316.²²⁴ After a significant exchange between Sanofi and FDA, on October 5, 2018 FDA approved the updated Taxotere label to add information from the 10-year follow-up to TAX316, including a description of persisting alopecia in the Adverse Reactions section of the label, but did not require a labeled Warning for persistent alopecia.²²⁵

While FDA was reviewing the RPR supplemental NDA application for TAX316 node positive breast cancer, RPR also submitted an application to add that indication to the approved uses of Taxotere in Europe. The Committee for Medicinal Products for Human Use (CHMP), the European Medicine's Agency (EMA) regulatory committee responsible for human drugs, approved Taxotere for adjuvant treatment of node positive breast cancer in 2004.²²⁶ While the CHMP acted to approve Taxotere for node positive breast cancer based on the results of TAX316, just as FDA did, unlike FDA, the CHMP also approved RPR's proposal to add to the Taxotere SmPC labeling information about adverse reactions persisting into the follow-up period, including ongoing alopecia.²²⁷ That risk information was added to the Undesirable effects (adverse reactions), not the Special Warnings and precautions section of the SmPC. Thus, at this point in time, the US and European labeling for Taxotere diverged on this point as a result of the decisions made not by Sanofi, but by the local regulatory authorities.

²²² Sanofi_00724262.

²²³ Sanofi_00262024.

²²⁴ Sanofi_05967367.

²²⁵ NDA 20-449/S-079, approval letter, Kordestani to Doty, October 5, 2018 and Taxotere label revised 10/2018.

²²⁶ Sanofi 05173852.

²²⁷ Sanofi_01094524.

This represents an example of how different regulatory authorities presented with the same data and information, can reach different decisions on appropriate product labeling.

C. GEICAM 9805 - Taxotere in Combination with Doxorubicin and Cyclophosphamide for the Adjuvant Treatment of Patients with Operable Node-Negative Breast Cancer

On November 30, 2009, Sanofi submitted Taxotere supplemental NDA S-060 to FDA to provide for Taxotere to be used in combination with doxorubicin and cyclophosphamide for the treatment of patients with operable node-negative breast cancer (node negative breast cancer). Included in that submission was clinical safety and efficacy data from the Phase III study [GEICAM 9805 or TAX301] “A Multicenter Phase III Randomized Trial Comparing Docetaxel in Combination with Doxorubicin and Cyclophosphamide (TAC) versus 5-Flurouracil in Combination with Doxorubicin and Cyclophosphamide (FAC) as Adjuvant Treatment of High Risk Operable Breast Cancer Patients with Negative Axillary Lymph Nodes”.²²⁸ This study also allowed for significant post-therapy follow-up of the patients because of the good post-therapy prognosis in this population. The study was designed for patients to be treated with six cycles of therapy and then followed for up to 10 years post-treatment. Thus, this study design also allowed for the analysis of long term-safety of those adverse events persisting into the follow-up period. This was possible because the overall survival of the TAC treated patients was 95.2% with a median follow-up time of 77 months.²²⁹ This is in contrast to the Taxotere previously-treated metastatic breast cancer trials in the original NDA where the survival of patients was much shorter, generally ranging about one year in duration.²³⁰ The supplemental NDA Clinical Summary of Safety noted in its analysis of TEAEs persisting into the follow-up period that “alopecia remained ongoing in 3 of 49 (6.1%) of TAC patients compared with 1 of 35 (2.9%) FAC patients.”²³¹ The follow-up in GEICAM9805 was not as robust as the follow-up in TAX316 as “TEAEs (treatment emergent adverse events) were followed into the follow-up period at the discretion of the investigator.”²³² Thus, the number of reported ongoing events was

²²⁸ Sanofi_00215728.

²²⁹ Sanofi_00384946.

²³⁰ Sanofi_00655001.

²³¹ Sanofi_00385012.

²³² NDA S-060, Clinical Summary of Safety, September 10, 2009, p. 34.

markedly smaller and the ability to determine frequencies of ongoing, or persistent, or irreversible alopecia from this study was minimized as compared to the TAX316 study.

With this November 30, 2009 supplemental NDA submission, Sanofi again proposed revisions to the Taxotere label to reflect this new proposed indication (node negative breast cancer) and other information from the clinical study. Specifically, in addition to another tabular listing of alopecia in the Adverse Reaction section of the labeling, Sanofi again proposed to add to the Adverse Reactions section of the label information about adverse reactions that persisted into the follow-up period of the study. Sanofi's labeling proposal for the Adverse Reactions section of the label was to add a subsection, "**Other persistent reactions**...The following events were observed to be ongoing in TAC-treated patients at the median follow-up time of 77 months; alopecia (n=3/49), amenorrhea (n=7/18), lymphoedema (4/5), peripheral sensory neuropathy (3/10)."²³³ (The patient labeling information about the risk of hair loss as described above was to be retained as described above.)

This Sanofi labeling proposal was not implemented because during the course of the review of the supplemental NDA, FDA raised concerns about the evolving standards of care in this patient population that occurred after the initiation of the study which would impact the approvability of the indication based upon the GEICAM 9805 study. That ultimately led to Sanofi's withdrawal of the supplement.²³⁴

Despite the withdrawal of the supplement, this represents another example of Sanofi presenting a clear analysis of data demonstrating the persistence of alopecia into a long-term follow-up period, well after the completion of Taxotere treatment. Additionally, it represents a further example of Sanofi advocating to FDA to include information in the Taxotere label describing persisting alopecia.

In Europe, Sanofi also submitted an application to include the node negative breast cancer indication for Taxotere based on the results of the GEICAM 9805 study. Unlike FDA, the European CHMP recommended the use of Taxotere in combination with doxorubicin and

²³³ Sanofi_00384656, p. 26.

²³⁴ Sanofi_00205084.

cyclophosphamide for adjuvant treatment of patients with operable node negative breast cancer node negative breast cancer as supported by GEICAM 9805 on May 20, 2010 (endorsed by the European Commission on July 6, 2010).²³⁵ The SmPC was amended later to add information about ongoing alopecia seen in this study in the Undesirable effects section as well.

This is a further example of different regulatory authorities making different decisions when presented the same data and information. Here the different decision-making is not just related to different labeling presentations, but the decision to actually approve or reject an indication in a critical clinical setting.

D. Periodic Safety Update Report for Docetaxel, January 21, 2011

In meeting its post-marketing pharmacovigilance obligations, on January 27, 2011 Sanofi submitted to FDA the January 21, 2011 PSUR for docetaxel.²³⁶ The report included PSUR numbers 27 and 28 with a bridging summary covering the period of December 1, 2009 through November 30, 2010.²³⁷ PSUR 28 provided worldwide safety information relating to Taxotere for the June 2010 to November 2010 time period.²³⁸

In the report, Sanofi identified persistent alopecia as a specific safety topic under review.²³⁹ Sanofi identified a request by the French Health Products Safety Agency (AFSSAPS) for an analysis of the Sanofi safety database and a literature search for reports of persistent alopecia associated with Taxotere.²⁴⁰ The resulting Clinical Overview Docetaxel – Persistent Alopecia was included in the PSUR.²⁴¹ This robust analysis of persistent alopecia (cases of alopecia persisting for 12 months or more after completion of chemotherapy) seen with Taxotere was a comprehensive analysis of the Sanofi global pharmacovigilance adverse event database augmented by a cumulative literature search.

²³⁵ Sanofi_01095353.

²³⁶ Sanofi_00201968.

²³⁷ Ibid.

²³⁸ Sanofi_00197757.

²³⁹ Sanofi_00197759, Sanofi_00197839.

²⁴⁰ Sanofi_00201052.

²⁴¹ Sanofi_00201046.

Sanofi performed a cumulative search from 1996 to 2010 of its global pharmacovigilance database including adverse events from Sanofi clinical studies (source = SS – sponsored study) as well as spontaneous reports (source = HCP – health care provider or Con – consumer) to detect all reports of alopecia.²⁴² Those reports were reviewed to identify cases reporting an outcome of alopecia at least 12 months following the last dose of chemotherapy including docetaxel which were considered cases of persistent alopecia.²⁴³ The twelve-month “cut-off” to measure persistent alopecia was selected by Sanofi as to be consistent with the request from the AFSSAPS, which noted a majority of cases of persistent alopecia ongoing more than 12 months after the end of chemotherapy.²⁴⁴ That was taken by Sanofi as “a clue that (persisted for longer than twelve months) could be one definition.”²⁴⁵ The twelve-month cut-off was not a bright line threshold. Reports with sufficient information to evince that the alopecia had not recovered for “11 months”, or “about 1 year”, “almost 1 year,” etc. were considered sufficiently close to the 12 months needed for the definition of persistent alopecia to be included²⁴⁶ “just to be on the safe side.”²⁴⁷ The author of the Clinical Overview, Dr. Palatinsky, explained, “I didn’t want to have any chance to miss any potential cases of interest that could have had, for example, 11 months of follow-up...So I wouldn’t be limited to the twelve months.”²⁴⁸ Dr. Palatinsky noted that in determining the 12 month criteria, “What I did was to search the literature...But there is no standardized definition of persistent alopecia,”²⁴⁹ and “There is no medical definition of (persistent alopecia). The literature is not consistent or uniform in regards of giving a specific number or months or weeks for alopecia to be determined to be irreversible.”²⁵⁰ The methodology employed by Sanofi in this analysis was transparent and clearly articulated in the submitted Clinical Overview, identifying cases that were included in and excluded from the analysis.

The use of other criteria for persistent alopecia, such as alopecia persisting only for six

²⁴² Sanofi_00201056.

²⁴³ Sanofi_00201057.

²⁴⁴ Sanofi_03643994.

²⁴⁵ Palatinsky deposition, August 9, 2018, p 515.

²⁴⁶ Sanofi_00201057.

²⁴⁷ Palatinsky deposition, August 9, 2018, pp. 291-292.

²⁴⁸ Ibid, pp. 515-516.

²⁴⁹ Ibid, p. 515.

²⁵⁰ Ibid, p. 293.

months following chemotherapy, at that time was not considered since the medical literature that has employed that potential definition of persistent alopecia is relatively recent, with the vast majority of the publications addressing that issue having been published subsequent to this 2011 analysis (e.g., Kim, G., et. al., Br Can Res Treat 163:527-533 (2017); Namini, S., J Clin Case Rep 6(8) (2016); Haider, M., et. al., J Cut Med & Surg 17(1):55-61 (2013), Kluger, N., et. al., Ann of Oncol 23(11):2879-2884 (2102)).

The AFSSAPS could have objected to such criteria and required Sanofi to complete a different analysis with different criteria for persistent alopecia, but did not do so.

Those reports of persistent alopecia were evaluated to determine if there was sufficient information for a medical assessment²⁵¹ and for factors such as age, diagnosis, concurrent anti-cancer treatment or other co-morbidities, time (or time lag) of onset of alopecia related to time of docetaxel administration, and ultimate recovery of alopecia.²⁵² The literature search was also comprehensive, surveying several recognized literature databases from 1996 to 2010 for literature reports of persistent alopecia with docetaxel.²⁵³ When asked about the exclusion of the Nabholz and Sedlacek publications from the literature review, Dr. Palatinsky explained, “The cases from the articles you mentioned are in our safety database. So they will be better analyzed in the body of the report without the need to duplicate them as literature review.”²⁵⁴

Sanofi evaluated the resulting 142 reports of persistent alopecia in its pharmacovigilance database and reported no evidence of a causal relationship with Taxotere alone because of co-administration of multiple anticancer agents known to cause alopecia, multiple co-morbidities associated with the onset of alopecia were reported, the time lag from the last dose of Taxotere and the onset of alopecia was occasionally prolonged, and the onset of alopecia occasionally pre-dated the administration of Taxotere. Sanofi concluded, “alopecia occurs very commonly (with Taxotere), though its persistence cannot be predicted and the available evidence does not show that irreversible alopecia is caused by docetaxel alone.”²⁵⁵

²⁵¹ Sanofi_00201057.

²⁵² Sanofi_00201057, Sanofi_00201063, Sanofi_00201087.

²⁵³ Sanofi_00201055.

²⁵⁴ Palatinsky deposition, August 9, 2108, p. 300.

²⁵⁵ Sanofi_00197757, p. 3,333.

Importantly, Sanofi also noted that three cases of persistent alopecia of at least one year in duration were reported as subsequently resolved in patients who were not otherwise different from those patients where the alopecia was reported as irreversible.²⁵⁶ Thus, caution must be applied when considering cases of persistent alopecia as representative of irreversible alopecia since some cases of persistent alopecia were subsequently resolved and, accordingly, are not truly cases of irreversible or permanent alopecia. Thus, considering reports of alopecia persisting only six months after the conclusion of therapy as irreversible is too conservative and to characterize such results as irreversible would be inaccurate, biased and misleading. Any reported frequency of irreversible alopecia derived from such a definition would be artificially inflated and also misleading. Indeed, Table 5 in Dr. Madigan's report notes that patients had resolution of alopecia after 12 months, after 24 months, and even after 60 months.

It is my opinion that this 2011 analysis by Sanofi of persistent alopecia with docetaxel was a thorough, reasonable, adequate and appropriate response to the French Health Product Safety Agency inquiry for such, consistent with applicable regulations and industry standards, and that it was also reasonable and appropriate for Sanofi to provide and highlight this analysis in its pharmacovigilance PSUR submission to FDA on January 27, 2011.

This same analysis of persistent alopecia was submitted to the European regulatory authority, the EMEA, on January 26, 2011.²⁵⁷ The Rapporteur (reviewer) concurred with Sanofi's assessment, "On the basis of the safety review, it is effectively difficult to conclude that docetaxel alone is able to induce persistent alopecia."²⁵⁸ Nonetheless, the Rapporteur recommended, "Given the number of cases reported in the post marketing surveillance, the EU SmPC should therefore be updated in order to address this risk more clearly."²⁵⁹ On September 28, 2011 Sanofi submitted proposed changes to the SmPC to include a statement that "Cases of persisting alopecia have been reported," in the Undesirable effects post-marketing experience section and a statement in the Patient Leaflet section on Possible

²⁵⁶ Ibid, p. 3,332.

²⁵⁷ Sanofi_01923983-94.

²⁵⁸ Sanofi_01113662.

²⁵⁹ Ibid.

effects, “Hair loss (in most cases hair growth should resume).”²⁶⁰ On December 15, 2011, the CHMP endorsed Sanofi’s proposed changes to the SmPC regarding persisting alopecia.²⁶¹

Unlike the European regulatory authorities, after receipt of this analysis of persistent alopecia FDA did not require Sanofi to make any labeling revisions to the US Taxotere label describing persistent alopecia at that time.

This is an example of the reasonable and appropriate postmarketing pharmacovigilance process by Sanofi and yet another example of Sanofi providing a thorough analysis of persistent alopecia to FDA. The issue of persistent alopecia was identified in the Executive Summary of the PSUR, was called out as a Specific Safety Topic Under Review in the Overall Safety Evaluation section of the report, and the full Clinical Overview was included as an appendix to the PSUR. This is a fulsome and forthright approach in presenting this issue and its analysis to FDA.

E. 2010 Labeling Change

On November 12, 2009, Sanofi submitted supplemental NDA S-059 to update the Taxotere labeling Pediatric Use and Human Pharmacokinetics sections of the labeling to incorporate the findings of pediatric studies.²⁶² Included in that supplement were Sanofi’s proposed revisions to the Taxotere label, which contemplated no changes to the Taxotere Patient Labeling. On May 3, 2010, FDA provided its recommendations on the Taxotere pediatric labeling proposal.²⁶³ In its recommendations FDA proposed revisions to the Sanofi labeling proposals for the Pediatric Use and Human Pharmacokinetics sections of the labeling, but also suggested significant revisions to the Taxotere Patient Labeling. FDA proposed to start the Patient Counseling Information section of the label with advice to the physician to, among other issues, “Explain to patients that side effects such as nausea, vomiting, diarrhea, constipation, fatigue, excessive tearing, infusion site reactions, and hair loss are associated with docetaxel administration.”²⁶⁴ Additionally, FDA proposed a major re-write of the patient labeling including a deletion of the information about hair loss: “*What are the*

²⁶⁰ Sanofi_01112272, Sanofi_05413055.

²⁶¹ Sanofi_00813022-23.

²⁶² Sanofi_00793355.

²⁶³ Sanofi_02986067.

²⁶⁴ Ibid, 62-70.

possible side effects of Taxotere? **Hair Loss** – Loss of hair occurs in most patients taking Taxotere (including the hair on your head, underarm hair, pubic hair, eyebrows and eyelashes). Hair loss will begin after the first few treatments and varies from patient to patient. Once you have completed all your treatments, hair generally grows back.” In its place, FDA proposed to include a single bullet point listing hair loss as one of the most common side effects of Taxotere and to add advice to the patient to “Tell your doctor if you have any side effect that bothers you or does not go away.” FDA also proposed to include a listing of the most common adverse reactions from Taxotere, including alopecia, at the beginning of the Adverse Reactions section of the labeling.²⁶⁵ The Clinical Trial Experience section of Adverse Reactions was otherwise unchanged as it addressed the reports of alopecia in the Taxotere clinical trials.²⁶⁶ After a series of exchanges between FDA and Sanofi, FDA approved this revised labeling, including the revised patient labeling proposed by FDA as described above, for Taxotere on May 13, 2010.²⁶⁷

To offer perspective on this FDA-initiated patient labeling change, it is noted that a similar labeling revision was implemented for Taxol (paclitaxel) in the same time frame. This likely reflects an approach at FDA to harmonize labeling for oncology agents, particularly taxanes, as possible. In its exchange with Sanofi described above, FDA noted, “It is a Division policy to maintain consistency for all cancer drug labels.”²⁶⁸

For Taxol, the Patient Labeling as of July 2000 was similar to that of Taxotere, “Hair Loss. Complete hair loss, or alopecia, almost always occurs with Taxol. This usually involves the loss of eyebrows, eyelashes and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. *Hair generally grows back after you’ve finished your Taxol treatment.*”²⁶⁹ In the subsequent August 2010 version of the Taxol labeling, approved, August 13, 2010, the patient labeling addressed hair loss as a single bullet point as one of the most common side effects of Taxol just as in the FDA-initiated change in the Taxotere patient labeling.²⁷⁰

²⁶⁵ Ibid, p. 19.

²⁶⁶ Ibid, pp. 19 – 38.

²⁶⁷ Sanofi_00793355.

²⁶⁸ Sanofi_00168582, p. 5.

²⁶⁹ NDA 20-262, S-037, Labeling Review, March 4, 2002.

²⁷⁰ NDA 20-262, S-048, approved August 13, 2010.

Another taxane formulation then on the market, Abraxane, showed a similar contemporaneous labeling change. In the Patient Labeling for Abraxane as of May, 2009 it was noted that “Complete hair loss, or alopecia, almost always occurs with Abraxane. This usually involves the loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. *Hair generally grows back after you’ve finished your Abraxane treatment.*”²⁷¹ In the subsequent December 2011 version of the Abraxane labeling, approved December 23, 2011, the patient labeling addressed hair loss as a single bullet point as one of the most common side effects of Abraxane just as in the FDA-initiated change in the Taxotere patient labeling.²⁷²

It is my opinion that it was reasonable for Sanofi to accept FDA’s proposed Patient Labeling changes respecting the Agency’s regulatory authority, particularly given that such labeling changes were implemented throughout the therapeutic category.

F. Taxotere European Labeling

As noted above, with the European approval of revised Taxotere labeling to reflect a new use for adjuvant treatment of node positive breast cancer based upon TAX316, in 2004, the SmPC then included information about persisting alopecia.²⁷³ Later the European authorities approved the use of Taxotere for adjuvant treatment of node negative breast cancer based on GEICAM 9805. Subsequently, the SmPC was amended to include the results of GEICAM 9805 as they related to ongoing alopecia. As described above, in December 2011, the SmPC was amended to note that “Cases of persisting alopecia have been reported,” in the Post-marketing experience (Undesirable effects) section of the label.²⁷⁴ Following several clarifying exchanges between Sanofi and the European regulators about the results of TAX316 and GEICAM 9805, the SmPC was updated by July 2015 to include a tabulated list of adverse reactions for adjuvant therapy with Taxotere including, “Alopecia (persisting: <3%)(very common).”²⁷⁵ In each of these labeling revisions, the European regulators required Sanofi to describe the risk of persisting alopecia in the Undesirable

²⁷¹ NDA 21-660, S-022, approved June 26, 2009.

²⁷² NDA 21-660, S-029, approved December 23, 2011.

²⁷³ Sanofi_01094524

²⁷⁴ Sanofi_05413055.

²⁷⁵ Sanofi_00829529.

effects section of the SmPC, not the Special warnings and precautions section.

Such differences in labeling between the European and US labels are not unusual, reflecting the individual regulatory review and approval processes and their independent evaluation of the underlying data.

G. Sanofi Company Core Data Sheet/Company Core Safety Information Versions

The first version (Version 1.0) of the Sanofi Taxotere Company Core Data Sheet issued after the May 14, 1996 US NDA approval, listed alopecia as an undesirable effect or an adverse reaction seen with an incidence of 79% in the initial clinical studies of locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or who have relapsed during anthracycline-based adjuvant therapy.²⁷⁶ [The safety information included in the versions of the Sanofi docetaxel CCDS was mirrored in the corresponding CCSI version.] That information remained essentially unchanged through Version 10.0, dated December 10, 2003.

With Version 11.0 of the Corporate Safety Data Sheet of February 5, 2004, Sanofi added to the CCDS section on Adverse Reactions, the information from TAX316 described above about Other persistent reactions, alopecia 22/687 observed ongoing at the median follow-up time of 55 months.²⁷⁷ This 2004 addition represents the first inclusion of information about persisting alopecia in the Taxotere reference safety documents. Despite FDA's rejection of Sanofi's proposed labeling for Taxotere to include this information about persisting alopecia in August 2004 as described above, Sanofi retained this information in the CCDS/CCSI in subsequent versions into 2009.

With Version 22 of the docetaxel CCDS dated September 9, 2009, Sanofi added to the CCDS section on Adverse Reactions, the information from GEICAM 9805 described above about Other persistent reactions, alopecia 3/49 observed ongoing at the median follow-up time of 77 months.²⁷⁸ The information from TAX316 about persisting alopecia remained

²⁷⁶ Sanofi_04798108.

²⁷⁷ Sanofi_01264126-42.

²⁷⁸ Sanofi_03277176-240.

unchanged.

With version 26 of the docetaxel CCDS dated June 28, 2011, Sanofi updated the Adverse Reactions section to reflect the language from the 10-year follow-up report of TAX316 described above noting that the most common adverse reactions persisting into the follow-up period in TAC treated patients were alopecia (92.3%).²⁷⁹ The information in the CCDS from GEICAM 9805 about persisting alopecia as described above remained unchanged.

With Version 29 of the docetaxel CCDS dated November 12, 2014, Sanofi updated the Adverse Reactions section to reflect the language from the 10-year follow-up report of GEICAM 9805 noting the most common adverse events persisting into the follow-up period (median follow-up time of 10 years and 5 months) were alopecia (49 patients, 9.2%).²⁸⁰ Also, that alopecia related to study drug started or worsened during the follow-up period in 42 patients (7.9%).²⁸¹

With Version 30 of the docetaxel CCDS dated November 16, 2015, Sanofi updated the Post-Marketing Experiences section of the Adverse Reactions section to note that “Cases of permanent alopecia (frequency not known) have been reported.”²⁸²

With Version 33 of the docetaxel CCDS dated March 16, 2017, Sanofi updated the Adverse Reactions section for persisting alopecia seen with TAX316 to note that 92.3% of the patients reported alopecia persisting into the follow-up period, but that 3.9% remained ongoing at the end of the follow-up period.²⁸³ The Adverse Reaction language for GEICAM 9805 was updated similarly to note that 9.2% of the patients reported alopecia persisting into the follow-up period, but that 0.6% remained ongoing at the end of the follow-up period.²⁸⁴

Thus, the Sanofi Taxotere CCDS and CCSI have always included alopecia as an adverse event and since 2004 the Taxotere CCDS and CCSI have consistently described data on persistent

²⁷⁹ Sanofi_00805192.

²⁸⁰ Sanofi_02399458-534.

²⁸¹ Ibid.

²⁸² Sanofi_01199744.

²⁸³ Sanofi_02399259-335.

²⁸⁴ Ibid.

alopecia in patients treated with Taxotere alongside other chemotherapy agents.

H. 2015 Labeling Change

On March 23, 2015, FDA contacted Sanofi and requested a “summary of cases of permanent partial or total alopecia associated with docetaxel use,” by April 10, 2015.²⁸⁵ No other perspective was provided by FDA at that time. On April 10, 2015, Sanofi submitted the requested response.²⁸⁶ The response included Sanofi’s search of its global pharmacovigilance database for reports of long-standing alopecia (e.g., permanent, persistent, irreversible, chronic) associated with Taxotere use, searching as far back as the introduction of Taxotere to the market in 1996. The search found 89 cases of “permanent alopecia (verbatim including terms such as “permanent”, “chronic” and “irreversible” and cases with alopecia lasting more than 2 years).²⁸⁷ Even with these rigorous criteria, Sanofi identified cases of such “permanent” alopecia where the alopecia subsequently recovered, questioning the adequacy of even two years of post-therapy follow-up to determine the “permanence” or “irreversibility” of such reports of alopecia.²⁸⁸ There were also numerous confounding factors in these cases. Sanofi concluded that “alopecia occurs very commonly. Permanent alopecia is mostly reported in female patients with breast cancer. The available evidence does not show that permanent alopecia is caused by docetaxel alone.”²⁸⁹

FDA performed its own independent analysis of Sanofi’s Response. At a minimum, it reviewed Sanofi’s submission and presented the data to two breast cancer review teams in May 2015.²⁹⁰ FDA determined “that virtually all of the described cases of alopecia were confounded by use of other cytotoxic agents, which are also known to cause alopecia.”²⁹¹ Nonetheless, after further internal discussions and “due to the possibility that permanent alopecia **may be** associated with docetaxel use,” FDA decided to request a Prior Approval Supplement from Sanofi to “update the docetaxel label, which already lists alopecia as a

²⁸⁵ Sanofi_01574962.

²⁸⁶ Ibid.

²⁸⁷ Sanofi_01259408.

²⁸⁸ Ibid, at p. 6.

²⁸⁹ Ibid, at p. 24.

²⁹⁰ Prowell, T. to Diggs, F., et. al., Congressional Response Letter – Taxotere Adverse Events, November 22, 2015.

²⁹¹ Ibid.

known adverse drug reaction, to indicate that alopecia may be permanent.”²⁹²

Six months after Sanofi’s initial submission, on October 2, 2015, FDA requested that Sanofi “[p]rovide any additional information regarding permanent or irreversible alopecia,” and “[a]mend the package insert in Section 6.2 (Adverse Reactions - Postmarketing Experience)(and patient information, if appropriate) to add information on permanent or irreversible alopecia,” within 60 days.²⁹³ In FDA’s judgment, the Taxotere labeling was to be revised to reflect reports of permanent alopecia in the Adverse Reactions section of the label, not the Warnings section. It should be noted that FDA did not require this new safety labeling under the provisions of Section 505(o)(4) of the FD&C Act (FDAAA) as a serious risk or unexpected serious risk.²⁹⁴

On November 24, 2015, Sanofi provided its response.²⁹⁵ Sanofi’s response included an updated Clinical Overview that evaluated docetaxel and permanent alopecia, reports with a verbatim event that included either “permanent” or “irreversible” or reports of alopecia that lasted more than 2 years with an outcome of not recovered/recovering/unknown.²⁹⁶ These 2015 requests from FDA were for a different analysis, for permanent alopecia, different from the 2010 request from the AFSSPAS for an analysis of persistent alopecia as described in section IV. D. of this report, that resulted in the 2011 PSUR. The 2011 analysis of persistent alopecia identified cases that persisted for at least 12 months following therapy, but then resolved such that such cases of persistent alopecia were not all true cases of permanent alopecia. Accordingly, different criteria, longer, more stringent criteria, were employed in the 2015 analysis of permanent alopecia. FDA could have objected to those criteria of permanent alopecia, but did not. Sanofi’s November 25, 2015 response also included, as requested by FDA, a Changes Being Effected (21 CFR 314.70(c)) labeling supplement to update the Post-Marketing Experiences in the Adverse Reactions section of the Taxotere labeling and a further update to the Patient Counseling and Patient Information labeling. The labeling proposal from Sanofi was to add “Cases of permanent alopecia have been reported,” to the Post-Marketing Experience section of the Adverse

²⁹² Ibid.

²⁹³ Sanofi_00805353.

²⁹⁴ Guidance for Industry, Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act, July 2013, p.3.

²⁹⁵ Sanofi_03333249.

²⁹⁶ Sanofi_01268143, at p. 12.

Reactions section of the label; to add that “cases of permanent hair loss have been reported,” to the Patient Counseling Information for Physicians section of the label; and to add to the listing of hair loss in the Patient Labeling, “In most cases normal hair growth should return. In some cases (frequency not known) permanent hair loss has been observed.”

In the updated Clinical Overview, Sanofi provided additional background on alopecia and its occurrence with anti-cancer agents and updated its review of the Sanofi global pharmacovigilance database to report 117 cases of “permanent alopecia,” the majority of which were treated with combination treatments including other agents known to induce alopecia.²⁹⁷ Sanofi also reiterated the results of TAX316 and GEICAM 9805 relative to persisting alopecia and reviewed the literature for pertinent studies. Sanofi conclusions included:

Alopecia is a very common adverse reaction of docetaxel.

Upon review of the safety database, 117 cases were considered permanent alopecia.

Of those cases, the majority received combination chemotherapy and/or hormonal therapy also known to cause alopecia.²⁹⁸

The frequency of permanent/irreversible alopecia is unknown as the number of patients exposed to docetaxel is unknown in post-marketing surveillance.

After having received FDA’s determination that a labeling change for Taxotere for permanent alopecia was to be implemented, Sanofi concluded that the cumulative weighted evidence was sufficient to support a causal association between docetaxel and permanent/irreversible alopecia, but that the benefit-risk relationship remains unchanged; the benefits of docetaxel continue to outweigh the risks, including permanent alopecia.²⁹⁹ The contributing Sanofi pharmacovigilance experts, Dr. Shang Jen and Dr. Nanae Hangai, explained in their respective depositions that this conclusion means that the evidence could not rule out the role of docetaxel in contributing to the occurrence of permanent alopecia in patients who receive therapy, mostly in combination with other chemotherapeutic agents, and that the conclusion does not mean that Taxotere is a proven cause of permanent

²⁹⁷ Ibid.

²⁹⁸ Ibid, p.35.

²⁹⁹ Ibid, pp. 35-36.

alopecia.³⁰⁰ (A - “That information shows that docetaxel often isn’t given alone, and because of that you can’t fully rule out that docetaxel may have the chance of causing it, but there’s also a lot of concomitant medications and confounding factors that cause alopecia – permanent or irreversible alopecia as well. So the company takes a more conservative point – stance, and says that, you know, we can’t completely rule it out, and that’s why there’s a causal relationship.” Q- ‘Does that mean that docetaxel alone causes permanent alopecia?’ A – “No, it does not. As I mentioned, based on the review, you know, we know that docetaxel oftentimes isn’t used alone, so that’s why we still state the causal association.” Q – “And does that conclusion mean that Taxotere is a proven cause of permanent alopecia?” A – “No, it does not.”³⁰¹) That is, Sanofi did not conclude medical causation for Taxotere and permanent alopecia. This position was echoed by Dr. Kopreski in his deposition testimony on the significant contribution of adriamycin and cyclophosphamide (AC) to the occurrence of persistent alopecia seen in patients treated with TAC.³⁰²

Again, FDA reviewed the data from the Clinical Overview. FDA concurred with Sanofi’s conclusion, “it’s impossible to determine whether the permanence of alopecia was due to docetaxel,”³⁰³ and “The Sponsor and FDA concur that the available evidence supports a **potential** causal association between docetaxel and permanent alopecia,”³⁰⁴ (emphasis added).

Three weeks later, on December 11, 2015, FDA approved this revised labeling for Taxotere with no further change.³⁰⁵ FDA continued to judge that the Taxotere labeling was adequate to allow for the safe use of the drug even with permanent alopecia labeled as an Adverse Reaction, not requiring it to be labeled as a Warning.

In terms of background on this labeling change, the FDA Medical Review notes that FDA’s March 23, 2015 request to Sanofi was stimulated by contact with oncology patient

³⁰⁰ Jen deposition, September 21, 2018, pp. 385-386, Hangai deposition, February 1, 2018, pp. 18, 194, 275-276.

³⁰¹ Jen deposition, September 21, 2018, pp. 385 – 386.

³⁰² Kopreski deposition, October 11, 2018, p. 764.

³⁰³ Prowell, T. to Diggs, F., et. al., Congressional Response Letter – Taxotere Adverse Events, December 4, 2015.

³⁰⁴ NDA 20-449, S-075, Medical Review, Prowell, T., December 4, 2015.

³⁰⁵ Sanofi_00836220.

advocates who acknowledged that the Taxotere label described alopecia as a common adverse reaction, but did not reflect that alopecia could be permanent.³⁰⁶ The Medical Review notes the concurrence of the reviewer with Sanofi's interpretation of the available evidence as described above, principally that the reports of permanent alopecia with Taxotere were confounded by the use of other cytotoxic agents which are also known to cause alopecia and "that the available evidence supports a potential causal association between docetaxel and permanent alopecia."³⁰⁷ FDA also notes, "the true incidence of permanent alopecia is unknown and cannot be reliably estimated given the limitations of the available data."³⁰⁸ The Medical Review also noted its agreement with Sanofi's labeling proposal.³⁰⁹ Ultimately, the medical reviewer specifically commented about the labeling proposal, "**I think the Sponsor's simple statement that permanent cases have been reported is all that can reliably be said given the tremendous limitations of the available data.**"³¹⁰

It is my opinion that Sanofi acted as a reasonable and responsible pharmaceutical sponsor in its response to FDA on this issue. Its analyses were timely, thorough, detailed and clear and based on appropriate pharmacovigilance systems and processes. The analyses provided a detailed assessment of the individual spontaneous adverse event reports as well as an assessment of those reports in aggregate and closed with Sanofi's overall analysis of the information. Sanofi's statement that the cumulative weighted evidence was sufficient to support a causal association between docetaxel and permanent/irreversible alopecia was intended to convey that because of the occurrences of such reports with Taxotere in combination therapy, the role of Taxotere as a potential causative agent could not be ruled out – medical causation for Taxotere alone and permanent alopecia was not determined. It is my opinion, and the stated opinion of the FDA, that Sanofi's assessment of the evidence was a reasonable and appropriate analysis of permanent alopecia associated with Taxotere administration, and that the analysis was confounded by the co-administration of other agents known to cause alopecia. It is also my opinion, and the stated opinion of FDA, that the labeling revision proposed by Sanofi to describe the potential risk of permanent

³⁰⁶ NDA 20-449, S-075, Medical Review, Prowell, T., December 4, 2015.

³⁰⁷ Ibid.

³⁰⁸ Ibid.

³⁰⁹ Ibid.

³¹⁰ Prowell, T. to Diggs, F., et. al., Congressional Response Letter – Taxotere Adverse Events, December 4, 2015.

alopecia with Taxotere was reasonable and appropriate and “all that can reliably be said given the tremendous limitation of the available data.”

Drs. Madigan and Kessler address the statement from Sanofi that the “cumulative weighted evidence is sufficient to support a causal association between docetaxel and permanent/irreversible alopecia,” and opine that this statement concludes a defined signal of causal association of Taxotere alone and irreversible alopecia (which it does not as described above) and that such a conclusion was available “several years earlier”³¹¹ or “as early as 2009.”³¹² Given the information presented in this report, I disagree. In 2004, Sanofi reported the results of the 55-month interim follow-up to TAX316 and reported on the frequency of ongoing alopecia following therapy in this study.³¹³ Sanofi did not find this to be a signal of a causal association between Taxotere and irreversible alopecia. It did propose to include information about ongoing alopecia, not irreversible alopecia, in the Taxotere labeling.³¹⁴ FDA did not judge this information to be a signal of a causal association of Taxotere with irreversible alopecia as it did not require labeling of Taxotere as such, and did not even support inclusion in the labeling information about ongoing alopecia.³¹⁵ The EMEA also did not judge this information to be a signal of a causal association between Taxotere and irreversible alopecia, but did support inclusion of information in the European labeling for Taxotere to describe ongoing alopecia.³¹⁶ Before and after the submission of the TAX316 55-month follow-up data, Sanofi conducted its pharmacovigilance of Taxotere as described in Section IV. J. of this report. Sanofi monitored for safety signals for alopecia. Dr. Palatinsky clarified, “We assess safety signals all the time, and not only persistent alopecia,”³¹⁷ “...our duty is to keep monitoring what happens in relation to docetaxel,” and “we were looking at irreversible alopecia, among other adverse events.”³¹⁸ Sanofi did not identify a signal of a casual association of Taxotere with irreversible alopecia and did not recommend labeling for Taxotere to such effect. The regulatory authorities (FDA and EMEA) continued to evaluate this pharmacovigilance

³¹¹ Madigan expert report, November 2, 2108, para. 54.

³¹² Kessler expert report, November 6, 2018, para 208.

³¹³ Sanofi_05597232.

³¹⁴ Sanofi_00355202.

³¹⁵ Sanofi_04539472.doc.

³¹⁶ Sanofi_01094524.

³¹⁷ Palatinsky deposition, August 9, 2018, pp. 279-280.

³¹⁸ Palatinsky deposition, August 10, 2018, p. 551.

information and also did not identify a signal of Taxotere associated with irreversible alopecia nor recommend labeling for Taxotere as such. In 2011, Sanofi evaluated the available information for an association of Taxotere with persistent alopecia, a less rigorous threshold than for irreversible alopecia, and concluded that the available evidence did not show that irreversible alopecia is caused by docetaxel alone.³¹⁹ FDA did not judge this information as a signal of a casual association between Taxotere and irreversible alopecia. EMEA also did not judge this information to be a signal of a causal association between Taxotere and irreversible alopecia, but did require labeling for Taxotere to describe persisting alopecia.³²⁰ By 2011, the pharmacovigilance of Taxotere for longer term alopecia largely reflected the impact of stimulating factors for such reports including the 2009 “media reports,”³²¹ the 2009 Bourgeois publication, the survey of French oncologists for persistent alopecia in breast cancer chemotherapy³²² and the label change in Europe to describe persistent alopecia.³²³ Finally, only in 2015, when Sanofi evaluated the available information for Taxotere and irreversible alopecia, did Sanofi and FDA concur that it was “impossible to determine whether the permanence of alopecia was due to docetaxel” and “the available evidence supports a potential causal association between docetaxel and permanent alopecia.”³²⁴ The Taxotere labeling was updated to reflect this potential casual association between Taxotere and permanent alopecia despite the significant impact of confounding factors in this analysis. Thus, Sanofi continuously evaluated the available information for a signal for Taxotere and a potential causal association with longer term alopecia, including irreversible alopecia, as did the FDA and European regulators and no potential signal of a casual association between Taxotere and irreversible alopecia was identified until the 2015 analysis. To opine that such a signal was available in 2009 or several years earlier than 2015 is not consistent with this evidence.

Dr. Sedlacek’s abstract, published in 2006, does not change this analysis. Dr. Sedlacek’s findings, while important and the subject of follow up by Sanofi pharmacovigilance and regulatory reporting, cannot be interpreted as a signal of irreversible alopecia. The abstract’s limited data set must be measured against the more fulsome data sets discussed

³¹⁹ Sanofi_00197757, p. 3,333.

³²⁰ Sanofi_01113662.doc.

³²¹ Palatinsky deposition, August 10, 2018, pp. 437-444.

³²² Bourgeois, H., et. al., Cancer Research 2009, 69(24 Suppl): Abstract nr 3174.

³²³ Sanofi_00813022.doc.

³²⁴ NDA 20-449, S-075, Medical Review, Prowell, T., December 4, 2015.

above.

I. Overall Labeling Changes for Taxotere

As described above, Sanofi worked in concert with FDA during the course of the FDA review of the original NDA for Taxotere to develop labeling that would provide adequate directions for use to allow for the safe and effective use of Taxotere for its intended use in the treatment of breast cancer. However, drug product labeling is a dynamic entity with changes being proposed, reviewed, approved by FDA and implemented in the market as a result of new information becoming available to the drug product sponsor and FDA.

Sanofi was actively engaged with FDA in evolving the labeling for Taxotere after its initial introduction into the market. For example, after the initial approval for Taxotere on May 14, 1996, Sanofi has received FDA approval on twenty-eight additional supplemental NDA revisions to the labeling³²⁵ to keep this information up-to-date, reflecting current information and knowledge about Taxotere to allow for its safe and effective use prior to the 2015 labeling change described above.

Collectively, these actions demonstrate the willingness of Sanofi to evaluate new information that becomes available to it and to request and secure FDA approval of labeling changes to ensure that its labeling remains adequate and appropriate to facilitate the safe use of Taxotere. In any of those instances, FDA could have required Sanofi to update the Taxotere labeling with new Adverse Reactions labeling to describe the potential risk of persistent or irreversible alopecia. It did not. In any of those instances, FDA could have required a new Warning to describe persistent or irreversible alopecia. It did not. Sanofi's judgment was that the Taxotere label and its description of the potential risk of alopecia was appropriate and provided adequate directions for the safe use of the product. That judgment was offered time and again to FDA and FDA did not disagree.

This process also reflects Sanofi's postmarketing surveillance activities and the translation of those activities into actions to revise the Taxotere label to ensure current information is

³²⁵

<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020449>.

included in product labeling following medical evaluation by the sponsor and concurrence by FDA.

Specifically, during the 1996 - 2015 timeframe Sanofi provided to FDA a summary and analysis of the safety information obtained from the spontaneous postmarketing adverse event reports and a description of the actions taken, such as labeling changes or a recommendation that no labeling changes were warranted, based upon those reports on an annual basis in its periodic adverse drug experience report (PADER) for Taxotere. Additionally, in its NDA annual reports to FDA Sanofi summarized the safety information that became available to it during the previous year from preclinical studies, from clinical studies, or from the published scientific literature and its recommendations for any labeling revisions based on the information or its recommendation that no labeling changes were warranted.

FDA could have but did not recommend updated labeling for Taxotere in either the Adverse Reactions section or the Warnings section of the label to reflect persistent alopecia based upon its review of the Sanofi Taxotere PADERs, PSURs and NDA Annual Reports. In fact, as described above, FDA rejected Sanofi's proposals to label Taxotere for the potential risk for persisting alopecia on several occasions, as early as 2004.

Thus, Sanofi continued to assess, evaluate and analyze the safety information available to it through its ongoing pharmacovigilance efforts, and recommend appropriate labeling revisions to FDA or to offer its medical judgment to endorse the continuing adequacy of the Taxotere labeling to FDA for its consideration throughout the time of Taxotere on the market since 1996.

J. Sanofi's Post-Marketing Surveillance

After the initial NDA approval for Taxotere in May 1996, Sanofi began its post-marketing surveillance or pharmacovigilance activities to meet its obligations under the regulations for postmarketing reporting of adverse drug experiences³²⁶ and other postmarketing reports.³²⁷ At the time of the initial NDA approvals, in the approval letters FDA could have,

³²⁶ 21 CFR 314.80.

³²⁷ 21 CFR 314.81.

but did not establish any extraordinary requirements for postmarketing surveillance (e.g., REMS) for Taxotere. FDA also did not require any specific Phase IV commitments to further explore the safety of Taxotere after its entry into the market or even after Sanofi reported persisting alopecia seen in the TAX316 and GEICAM 9805 studies.

In its pharmacovigilance following the initial approval of Taxotere, Sanofi noted reports of alopecia and even reports of persistent alopecia in patients taking Taxotere and reported those findings in its postmarketing safety reports. Since the initial labeling for Taxotere as it was introduced to the market included alopecia as a labeled adverse reaction, reports of alopecia were considered expected under 21 CFR 314.80(a) and would not require a postmarketing 15-day Alert Report under 21 CFR 314.80(c)(1)(i), but would rather be reported in the periodic adverse drug experience report (PADER) as per 21 CFR 314.80(c)(2).

In its postmarketing reporting, Sanofi provided a summary of the information obtained from spontaneous postmarketing adverse event reports and a description of recommended labeling actions or a recommendation for no changes to the labeling as described above in section III. A. 5. of this report.

Thus, it is my opinion that Sanofi's postmarketing surveillance and evaluation of reports of alopecia and persistent alopecia associated with Taxotere therapy from the introduction of the product to the market in 1996, up to the time of the 2015 US labeling revision and through the life of the product to address permanent alopecia were thorough, appropriate, reasonable and in keeping with applicable regulations and industry standards.

K. Taxotere Advertising and Promotion Oversight

From the time of its initial approval on May 14, 1996 until the present, Sanofi (and its predecessor companies) has received several enforcement letters from FDA's DDMAC relating to its promotion of Taxotere. None of those enforcement letters addressed the promotion of Taxotere in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer ("adjuvant use") and the focus of those enforcement actions was not related to the discussion of the risk of alopecia or persistent or permanent alopecia in Taxotere promotional materials.

One enforcement action from DDMAC warrants comment. This DDMAC enforcement letter regarding Taxotere promotion was an Untitled Letter and was issued on April 16, 2009 to Sanofi.³²⁸ In this letter DDMAC claims that Sanofi presented unsubstantiated superiority claims vs. paclitaxel and overstates the efficacy of Taxotere in locally advanced or metastatic breast cancer in a reprint carrier describing the published results of study TAX 311.³²⁹ DDMAC noted that the study did not demonstrate a statistically significant advantage for Taxotere vs. paclitaxel on the primary study endpoint (overall response rate in the intent-to-treat population), that the promotional claims of superiority were based upon secondary endpoints and that the study had not been replicated as required to support a promotional claim for superiority.³³⁰ DDMAC requested Sanofi to cease dissemination of the reprint carrier and to respond in writing to its letter.³³¹

Sanofi responded on April 29, 2009 with a significant review of the prior correspondence between Sanofi and FDA on the use of TAX 311 (a study conducted to fulfill a FDA post-marketing commitment to compare Taxotere and paclitaxel in metastatic breast cancer) data in promotional materials.³³² The reprint carrier and the publication of the results of the TAX311 study demonstrated the “efficacy advantages for Taxotere over paclitaxel, including a significant improvement in the primary endpoint of objective response rate in the evaluable population, significant advantages in the secondary endpoint of time-to-progression in both the intent-to-treat and evaluable populations, and significant advantages in the secondary endpoint of survival in both the intent-to-treat and evaluable populations.”³³³ The primary study endpoint, which was the focus of the DDMAC letter, was the objective response rate in the intent-to-treat study population.³³⁴ In the cited reprint, the authors noted that, “the overall response rate (ORR, 32% vs 25%; $P = .10$) was higher for docetaxel.”³³⁵ The authors concluded, “docetaxel demonstrated superior efficacy compared with paclitaxel, providing significant clinical benefit in terms of survival and time to disease progression, with a numerically higher response rate and manageable

³²⁸ Sanofi_00337551.

³²⁹ Ibid.

³³⁰ Ibid.

³³¹ Ibid.

³³² Sanofi_04744172.

³³³ Ibid, p. 26.

³³⁴ Sanofi_00337551, p. 3.

³³⁵ Jones, S., et. al., J Clin Oncol 23:5542-5551.

toxicities.”³³⁶ Thus, Sanofi believed this information was important to “fully characterize this important drug so that prescribers can use it in as safe and efficacious manner as possible...helping them understand how to use Taxotere,” and “that the TAX311 data are consistent with our approved prescribing information,” and that the information was appropriate for promotional dissemination.³³⁷

In its April 29, 2009 response, Sanofi also noted that FDA had accepted TAX 311 to fulfill a post-marketing commitment requested by FDA, that Sanofi had advised FDA that it intended to employ TAX 311 in promotion of Taxotere since the data are consistent with the approved labeling for Taxotere in the treatment of metastatic breast cancer and that it had attempted to meet with FDA on several occasions to explore this issue, and that due to logistical issues associated with the age of study TAX 311, Sanofi could not file a labeling supplement to include the results of study TAX 311 in the Taxotere label.³³⁸ Nonetheless, Sanofi agreed to discontinue the reprint carrier and other promotional materials that include superiority claims for Taxotere vs. paclitaxel based on TAX 311, but would continue to disseminate information about the results of TAX 311 that avoids the claims of superiority vs. paclitaxel since Sanofi believes that the TAX 311 results are consistent with the FDA-approved Taxotere labeling.³³⁹

DDMAC responded on August 4, 2009, advised Sanofi to submit proposed promotional materials for Taxotere that contain claims based on TAX 311 for advisory comments and noted that, given Sanofi’s actions to discontinue use of the reprint carrier and related promotional materials, the matter was considered closed.³⁴⁰

In the intervening nine years, there have been no further FDA enforcement letters to Sanofi relating to the promotion of Taxotere, including any citations of inappropriate promotional comparisons with paclitaxel. It is my opinion that the receipt of only several enforcement letters over the course of 22 years that Taxotere has been on the market in a highly competitive, technically and medically complex field, is not indicative of a violative, non-complaint promotional approach. The enforcement citations for Taxotere promotion that

³³⁶ Sanofi_04744172.

³³⁷ Sanofi_04744174.

³³⁸ Ibid.

³³⁹ Ibid.

³⁴⁰ Sanofi_00356704.

were made by DDMAC were not related to its use in the adjuvant breast cancer treatment setting, the use of focus in this litigation, and the citations did not claim inadequate disclosure of the potential risk of persistent or permanent or irreversible alopecia associated with Taxotere use. Given the above and the absence of DDMAC enforcement action for Taxotere for adjuvant breast cancer use despite extensive promotion for such use, it is my opinion that the promotion of Taxotere, particularly for its use in the adjuvant breast cancer treatment setting, has been reasonable, appropriate, consistent with industry standards and applicable FDA regulations.

L. Multiple Submissions of Data/Analyses of Persistent Alopecia Seen with Taxotere Reported to FDA by Sanofi

Sanofi provided many submissions of data and analyses of the occurrence of persisting or persistent alopecia seen with Taxotere treatment before the 2015 revision to the label to note the occurrence of cases of permanent hair loss. Such submissions included:

- The March 17, 2004 submission of Taxotere supplemental NDA S-029 for Taxotere use in combination with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive breast cancer, including the clinical study report for TAX316 which noted an analysis of persistent adverse reactions, including the finding that 3.2% of TAC-treated patients showed alopecia that remained ongoing in the follow-up period for the patients in this interim analysis.³⁴¹ These results were presented in the Study Synopsis, Safety Results, Safety Summary and Discussion sections of the CSR in both tabular and text descriptions.³⁴² As described above in Section IV. B. of this report, Sanofi also proposed (in several filings) to include this description of persisting alopecia in the Taxotere labeling at this time,³⁴³ a proposal that was rejected by FDA.³⁴⁴
- The November 30, 2009 submission of Taxotere supplemental NDA S-060 for Taxotere use in combination with doxorubicin and cyclophosphamide as

³⁴¹ Sanofi_00798650.

³⁴² Ibid.

³⁴³ Sanofi_00355202.

³⁴⁴ Sanofi_04817139, Sanofi_04539472.doc.

adjuvant treatment of operable node-negative breast cancer, including the clinical study report for GEICAM 9805 which noted an analysis of persistent adverse reactions including the finding that 3 of 49 (6.1%) of the TAC treated patients showed alopecia that remained ongoing in the follow-up period for the patients in this interim analysis.³⁴⁵ Once again, the analysis of persisting alopecia was highlighted and presented in the Clinical Overview and the Clinical Summary of Safety included in the submission as well as in the clinical study report. As described in section IV. C. of this report, Sanofi again proposed to include a description of persisting alopecia in the Taxotere labeling with this filing.³⁴⁶ Sanofi's labeling proposal was not implemented because Sanofi subsequently withdrew the supplement as a result of FDA's concerns about the interpretability of the study given evolving standards of care in this patient population.³⁴⁷

- The September 24, 2010 submission³⁴⁸ of an updated clinical study report for TAX316 containing the 10-year follow-up data including an analysis that showed that 4.2% of the TAC treated patients demonstrated alopecia that remained ongoing in the follow-up period.³⁴⁹ Again, these results were presented in the Study Synopsis, Safety Results, Safety Summary and Discussion sections of the CSR in both tabular and text descriptions to provide a fulsome presentation of this information pertaining to persisting alopecia.³⁵⁰
- The January 27, 2011 submission of the January 21, 2011 PSUR for docetaxel. As described in Section IV. D. of this report, this PSUR identified persistent alopecia as a specific safety topic under review³⁵¹ and provided a thorough and detailed analysis of the Sanofi global pharmacovigilance adverse event database augmented by a cumulative literature search for

³⁴⁵ Sanofi_00215728.

³⁴⁶ Sanofi_00384656.

³⁴⁷ Sanofi_03242135.

³⁴⁸ Sanofi_01288423.

³⁴⁹ Sanofi_00724262.

³⁵⁰ Ibid.

³⁵¹ Sanofi_00197757.

reports of persistent alopecia in patients treated with Taxotere.³⁵² Sanofi concluded that the available evidence did not show that irreversible alopecia was caused by docetaxel alone.³⁵³

- The January 27, 2011 submission of the January 21, 2011 PSUR 28 also included, as part of the PSUR, the Sanofi Docetaxel Company Core Safety Information Version 24, dated December 14, 2009 as the reference safety information for Taxotere.³⁵⁴ This CCSI included the results of TAX316 and GEICAM 9805 regarding persisting alopecia.³⁵⁵
- The January 27, 2011 submission of the July 23, 2010 PSUR 27 also included, as part of the PSUR, the Sanofi Docetaxel Company Core Safety Information Version 23, dated October 1, 2009 as the initial reference safety information for Taxotere.³⁵⁶ This CCSI also included the results of TAX316 and GEICAM 9805 regarding persisting alopecia.
- The March 20, 2006 submission of PSURs 17 and 18 for Taxotere NDA 20-449.³⁵⁷ These PSURs included Sanofi CCSI Versions 13 (dated August 25, 2004), 14 (dated December 22, 2004), and 15 (dated July 20, 2005) as the reference safety information for Taxotere at that time.³⁵⁸ These CCSIs included the results of TAX316 regarding persisting alopecia.³⁵⁹
- The January 25, 2007, submission of PSURs 19 and 20 for Taxotere NDA 20-449.³⁶⁰ These PSURs included the Sanofi CCSI Versions 15(dated July 20, 2005) and 16 (dated April 5, 2006) as the reference safety information for

³⁵² Ibid.

³⁵³ Ibid, p. 3333.

³⁵⁴ Sanofi_00197904-44.

³⁵⁵ Sanofi_00197924, 26.

³⁵⁶ Sanofi_00194855.

³⁵⁷ Sanofi_00338117.

³⁵⁸ Sanofi_02399899, Sanofi_02399918, Sanofi_02399863.

³⁵⁹ Sanofi_02399911, Sanofi_02399930, Sanofi_02399876.

³⁶⁰ Sanofi_00337958.

Taxotere at that time.³⁶¹ These CCSIs included the results of TAX 316 regarding persisting alopecia.³⁶²

- The January 28, 2008 submission of PSURs 21 and 22 for Taxotere NDA 20-449.³⁶³ These PSURs included the Sanofi CCSI Versions 17 (dated December 7, 2006), 18 (dated February 14, 2007), and 19 (dated November 26, 2007) as the reference safety information for Taxotere at that time.³⁶⁴ These CCSIs included the results of TAX 316 regarding persisting alopecia.³⁶⁵
- The January 28, 2009 submission of PSURs 23 and 24 for Taxotere NDA 20-449.³⁶⁶ These PSURs included the Sanofi CCSI Versions 19 (dated November 26, 2007), 20 (dated August 26, 2008) and 21 (dated October 23, 2008) as the reference safety information for Taxotere at that time.³⁶⁷ These CCSIs included the results of TAX 316 regarding persisting alopecia.³⁶⁸
- The January 28, 2010 submission of PSURs 25 and 26 for Taxotere NDA 20-449.³⁶⁹ These PSURs included the Sanofi CCSI Versions 21 (dated October 23, 2008), 22 (dated September 9, 2009) and 23 (dated October 1, 2009) as the reference safety information for Taxotere at that time.³⁷⁰ These CCSIs included the results of TAX 316 and GEICAM 9805 regarding persisting alopecia.³⁷¹
- The January 26, 2012 submission of PSURs 29 and 30 for Taxotere NDA 20-449.³⁷² These PSURs included the Sanofi CCSI Versions 24 (dated December

³⁶¹ Sanofi_00288689, Sanofi_00286018.

³⁶² Sanofi_02399876, Sanofi_00288775.

³⁶³ Sanofi_00337580.

³⁶⁴ Sanofi_00387684, Sanofi_00385608.

³⁶⁵ Sanofi_00387776, Sanofi_00387799, Sanofi_00385723.

³⁶⁶ Sanofi_00231192.

³⁶⁷ Sanofi_00231203, Sanofi_00233554.

³⁶⁸ Sanofi_00231292, Sanofi_00233676, Sanofi_00233707.

³⁶⁹ Sanofi_00207641.

³⁷⁰ Sanofi_00207658, Sanofi_00210524.

³⁷¹ Sanofi_00207778, Sanofi_00210673, Sanofi_00210706.

³⁷² Sanofi_00183764.

14, 2009), 25 (dated April 4, 2011), and 26 (dated June 28, 2011) as the reference safety information for Taxotere at that time.³⁷³ These CCSIs included the results of TAX 316 and GEICAM 9805 regarding persisting alopecia.³⁷⁴

- The January 28, 2013 submission of PSURs 31 and 32 for Taxotere NDA 20-449.³⁷⁵ These PSURs included the Sanofi CCSI Versions 26 (dated June 28, 2011) and 27 (dated July 17, 2012) as the reference safety information for Taxotere at that time.³⁷⁶ These CCSIs included the results of TAX 316 and GEICAM 9805 regarding persisting alopecia.³⁷⁷
- The February 7, 2014 submission of the Periodic Benefit-Risk Evaluation Report (December 01, 2012 – November 30, 2013) for Taxotere NDA 20-449.³⁷⁸ This PBRER included the Sanofi CCSI Version 28, dated March 5, 2013 as the reference safety information for Taxotere at that time.³⁷⁹ This CCSI included the results of TAX 316 and GEICAM 9805 regarding persisting alopecia.³⁸⁰
- The February 6, 2015 submission of the Periodic Benefit-Risk Evaluation Report (December 01, 2013 – November 30, 2014) for Taxotere NDA 20-449.³⁸¹ This PBRER included the Sanofi CCSI Version 29, dated November 12, 2014 as the reference safety information for Taxotere at that time.³⁸² This CCSI included the results of TAX 316 and GEICAM 9805 regarding persisting alopecia.³⁸³

³⁷³ Sanofi_00183790, Sanofi_00180262.

³⁷⁴ Sanofi_00183926, Sanofi_00183966, Sanofi_00180442.

³⁷⁵ Sanofi_00174095.

³⁷⁶ Sanofi_00380160, Sanofi_00174101.

³⁷⁷ Sanofi_00380304, Sanofi_00174289.

³⁷⁸ Sanofi_00268919.

³⁷⁹ Sanofi_00172097.

³⁸⁰ Sanofi_00172288.

³⁸¹ Sanofi_00266009.

³⁸² Sanofi_00170301.

³⁸³ Sanofi_00170443.

At any of these instances, FDA could have, but did not determine that information on persisting or persistent or permanent or irreversible alopecia constituted a serious or otherwise clinically significant adverse experience such that a Warning would be appropriate to allow for the safe use of Taxotere. The labeling in effect describing alopecia in the Adverse Reactions section of the labeling was determined to be appropriate and to provide adequate directions for the safe use of Taxotere in the treatment of varying forms of breast cancer.

Based upon this extensive, thorough reporting to FDA on persisting and persistent alopecia and Taxotere, it is my opinion that Sanofi acted reasonably and appropriately and provided a fulsome and forthright reporting of this issue to FDA well before the 2015 US labeling change, beginning as early as 2004. FDA continued to accept the adequacy and appropriateness of the Taxotere labeling to allow for the safe use of the product, with alopecia described in the Adverse Reactions section of the labeling, without further characterization of the adverse reaction as chronic or persistent or permanent or irreversible, despite continued presentation of clinical data, spontaneous adverse events and CCSIs as core reference safety information describing reports of persisting and persistent alopecia, until it required the 2015 labeling change for cases of permanent alopecia having been reported.

V. Conclusion/Opinions

Based upon the above review, it is my opinion that Sanofi acted reasonably and appropriately in managing and conveying data and reports of alopecia and persistent or permanent alopecia and Taxotere, employing appropriate pharmacovigilance processes, in compliance with FDA regulations and consistent with pharmaceutical industry best practices.

It is also my opinion that, from the very beginning of the market introduction of Taxotere, that Sanofi consistently and comprehensively reported data on alopecia to FDA in a fulsome and forthright manner, consistent with the practices of a reasonable and responsible pharmaceutical sponsor to allow FDA to meet its role in the collaborative, ongoing safety assessment of the product.

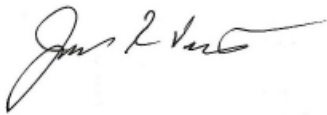
It is also my opinion that Sanofi acted reasonably, appropriately and with urgency to clearly respond to regulatory authority inquiries about the potential risk of alopecia and persistent or permanent alopecia with Taxotere.

It is also my opinion that Sanofi reasonably and appropriately labeled for alopecia in Taxotere labeling at all times as an Adverse Reaction, not a Warning, consistent with pharmaceutical product labeling regulations and with the judgment of the regulatory authorities to provide adequate directions for the product to be safely used for its approved indications and that Sanofi demonstrated a willingness to consider appropriate labeling revisions at all times with the regulatory authorities.

It is also my opinion that Sanofi reasonably and appropriately promoted Taxotere for adjuvant breast cancer treatment consistent with the labeling described above, in compliance with FDA regulations and consistent with industry practices.

This report represents the opinions I have formed in this matter to date. It reflects my review of the materials listed in Exhibit C and my experience in drug development and regulatory affairs in the pharmaceutical industry. I reserve the right to revise or amend my opinions based upon new information that might arise in the course of this case or my continuing assessment of the materials already reviewed. If called to testify at trial, I may further explain the opinions, principles, and terminology contained in this report and the cited materials reviewed. The opinions offered herein are made to a reasonable degree of professional regulatory probability.

Submitted,



Justin R. Victoria

December 28, 2018

EXHIBIT N

1 UNITED STATES DISTRICT COURT
2 EASTERN DISTRICT OF LOUISIANA

3 CASE NO. 2:16-cv-15859

4 CYNTHIA THIBODEAUX,
5 Plaintiffs,
6 v.
7 SANOFI S.A., SANOFI-AVENTIS U.S. L.L.C., SANOFI
8 US SERVICE, INC., and AVENTIS-PHARMA S.A.,
9 Defendants.

10 Deposition of CYNTHIA ANN THIBODEAUX, 1600
11 NORTH DORGENOIS STREET, NEW ORLEANS, LOUISIANA
12 70119, taken in the offices of MORRIS BART &
13 ASSOCIATES, on Thursday, December 14, 2017.

14 APPEARANCES:

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35 ATTORNEYS FOR PLAINTIFF

1 don't remember.

2 Q. By 2009?

3 A. Maybe '10.

4 Q. You think by 2010, your hair had reached the
5 level of regrowth that it's at today?

6 A. It's possible, yes.

7 Q. Well, possible doesn't --

8 MS. BIERI:

9 You understand why I'm asking these
10 questions. Right?

11 MR. MAHER:

12 I understand that. Are you asking me
13 to speak?

14 MS. BIERI:

15 Yeah.

16 MR. MAHER:

17 Okay. If you're inviting me to
18 speak, I don't want to say anything
19 that's going to get me in trouble with
20 the judge, but if you're asking me --

21 MS. BIERI:

22 Well, you sighed audibly on the
23 record and you gave me a face, and so I
24 asked you if you understood why I was
25 asking the questions. That's why I said

1 Q. Do you -- do you think -- I'm trying -- okay.

2 You say that you expected your hair to come
3 out during chemotherapy. Right?

4 A. Correct.

5 Q. And it did. Correct?

6 A. It did.

7 Q. But you're saying that you think your hair
8 should have come back. Correct?

9 A. Yes.

10 Q. And that's what you're seeking compensation
11 for in this litigation. Correct?

12 A. Correct.

13 Q. I have to know when you think your hair should
14 have come back.

15 When do you think your hair should have
16 come back?

17 MR. MAHER:

18 Okay.

19 MS. BIERI:

20 You can answer.

21 THE WITNESS:

22 I thought -- but I'm not a medical
23 person. I thought it was going to come
24 back after chemo, once chemo's
25 completed, maybe a few months later.

1 EXAMINATION BY MS. BIERI:

2 Q. That's what you expected, for your hair to
3 come back a few months after chemo was
4 completed?

5 A. Uh-huh.

6 Q. And it didn't do that?

7 A. Did not do that.

8 Q. Okay. Let's talk about -- have you ever
9 talked to anyone about your hair loss?

10 A. A professional person or just a friend or
11 family member?

12 Q. You know, that's a great question, Ms.
13 Thibodeaux. Did you ever talk to a doctor
14 about the hair loss that you're claiming in
15 this lawsuit?

16 A. No.

17 Q. Never sought to ask if there were any
18 treatment options available?

19 A. No, I didn't.

20 Q. Why not?

21 A. I just didn't think about it. I keep -- I
22 continued to think that it would come back
23 full as on one of these pictures, I didn't
24 think it would be like this for this length of
25 time.

EXHIBIT O

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

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CYNTHIA THIBODEAUX, CASE NO.
Plaintiff, 2:16-cv-15859

v.
SANOFI S.A., SANOFI-AVENTIS
U.S. L.L.C., SANOFI US
SERVICE, INC., AND
AVENTIS-PHARMA S.A.,

Defendants.

* * * * *

Deposition of
Cynthia Thibodeaux
taken on September 6, 2019
commencing at 9:10 a.m.

at the
offices of
Morris Bart, LLC
601 Poydras Street, Floor 24
New Orleans, Louisiana

1 A. No.

2 Q. Did Dr. Tosti ask you or did you tell
3 her about how your hair grew back in?

4 A. I don't recall.

5 Q. No recollection of that happening?

6 A. No.

7 Q. You didn't tell her that your hair grew
8 back to the level it is today by 2010?

9 A. I may have --

10 MR. ROOT: Object as to form.

11 A. I may have. I just don't recall at this
12 time.

13 Q. But you agree that your hair did grow
14 back to the level that it is today by the beginning
15 of 2010; correct?

16 A. Let me think about that.

17 That could be correct.

18 Q. That's right?

19 A. Yeah, I would say that was right.

20 Q. So by the beginning of 2010, you're not
21 seeing any more improvements to the regrowth
22 density-wise of your hair; right?

23 A. Right.

24 Q. Okay. Did you talk to Dr. Tosti about
25 your use of tamoxifen?

EXHIBIT P

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL)
PRODUCTS LIABILITY
LITIGATION

MDL NO. 2740

SECTION "H" (5)

THIS DOCUMENT RELATES TO
ALL CASES

TWELFTH AMENDED PLAINTIFF FACT SHEET

This Fact Sheet must be completed by each plaintiff who has filed a lawsuit related to the use of Taxotere® by the plaintiff or a plaintiff's decedent. Please answer every question to the best of your knowledge. In completing this Fact Sheet, you are under oath and must provide information that is true and correct to the best of your knowledge. If you cannot recall all of the details requested, please provide as much information as you can. You must supplement your responses if you learn that they are incomplete or incorrect in any material respect.

In filling out this form, please use the following definitions: (1) **"healthcare provider"** means any hospital, clinic, medical center, physician's office, infirmary, medical or diagnostic laboratory, or other facility that provides medical, dietary, psychiatric, or psychological care or advice, and any pharmacy, weight loss center, x-ray department, laboratory, physical therapist or physical therapy department, rehabilitation specialist, physician, psychiatrist, osteopath, homeopath, chiropractor, psychologist, nutritionist, dietician, or other persons or entities involved in the evaluation, diagnosis, care, and/or treatment of the plaintiff or plaintiff's decedent; (2) **"document"** means any writing or record of every type that is in your possession, including but not limited to written documents, documents in electronic format, cassettes, videotapes, photographs, charts, computer discs or tapes, and x-rays, drawings, graphs, phone-records, non-identical copies, and other data compilations from which information can be obtained and translated, if necessary, by the respondent through electronic devices into reasonably usable form.

Information provided by plaintiff will only be used for purposes related to this litigation and may be disclosed only as permitted by the protective order in this litigation. This Fact Sheet is completed pursuant to the Federal Rules of Civil Procedure governing discovery (or, for state court case, the governing rules of civil of the state in which the case is pending).

I. CORE CASE INFORMATION

Attorney Information

Please provide the following information for the civil action that you filed:

1. Caption: Cynthia Thibodeaux v. Sanofi-Aventis U.S., Inc., et al.
2. Court and Docket No.: USDC, EDLA 2:16-cv-15859-KDE-MBN
3. MDL Docket No. (if different): 2:16-md-02740-KDE-MBN

4. Date Lawsuit Filed: 10/26/16
5. Plaintiff's Attorney: Betsy Barnes
6. Plaintiff's Law Firm: Morris Bart, LLC
7. Attorney's Address: 601 Poydras Street 24th floor
New Orleans, LA 70130
8. Attorney's Phone Number: (504) 599-3234
9. Attorney's Email Address: bbarnes@morrisbart.com

Plaintiff Information

Please provide the following information for the individual on whose behalf this action was filed:

10. Name: THIBODEAUX, CYNTHIA
11. Street Address: [REDACTED]
12. City: [REDACTED]
13. State: [REDACTED]
14. Zip code: [REDACTED]
15. Date of Birth: [REDACTED]
16. Place of Birth: [REDACTED]
17. Social Security Number: [REDACTED]
18. Maiden or other names you have used or by which you have been known:
N/A
19. Sex: Male: ☐ Female: ☒
20. Race:

Race	Yes
American Indian or Alaska Native	<input type="checkbox"/>
Asian	<input type="checkbox"/>
Black or African American	<input checked="" type="checkbox"/>
Native Hawaiian or Other Pacific Islander	<input type="checkbox"/>
White	<input type="checkbox"/>

21. Ethnicity:

Ethnicity	Yes
Hispanic or Latino	<input type="checkbox"/>
Not Hispanic or Latino	<input checked="" type="checkbox"/>

22. Primary Language: English

Representative Information

If you are completing this questionnaire in a representative capacity (e.g., on behalf of the estate of a deceased person), please state the following:

23. Name:
24. Address:
25. Capacity in which you are representing the individual:
26. If you were appointed as a representative by a court, identify the State, Court and Case Number:
 - a) State:
 - b) Court:
 - c) Case Number:
27. Relationship to the Represented Person:
28. State the date of death of the decedent: --/--/----
29. State the place of death of the decedent:
30. Are you filling this questionnaire out on behalf of an individual who is deceased and on whom an autopsy was performed? Yes ☐ No ☐

If you are completing this questionnaire in a representative capacity, please respond to these questions with respect to the person whose medical treatment involved Taxotere® or Docetaxel.

II. PERSONAL INFORMATION

Relationship Information

Please provide the following information for the civil action that you filed:

1. Are you currently: Married: ☒ Single: ☐ Engaged: ☐
Significant other: ☐ Divorced: ☐ Widowed: ☐ Same sex partner: ☐
2. Have you ever been married? Yes ☒ No ☐
3. If yes, for EACH marriage, state the following:

Spouse's Name	Dates of Marriage	Date Marriage Ended	Nature of Termination
Williams, Frank		--/--/----	

Education

4. For each level of education you completed, please check below:
High School: ☒ Vocational School: ☐
College: AA: ☐ BA/BS: ☒ Masters: ☒ PhD: ☐ M.D.: ☐
Other:

Employment

5. Are you currently employed? Yes ☒ No ☐
6. If yes, state the following:
- a) Current employer name: Family Service of New Orleans
 - b) Address: 2515 Canal Street
New Orleans, LA 70113
 - c) Telephone number: (504) 822-0800
 - d) Your position there: Social worker
7. Are you making a claim for lost wages or lost earning capacity?
Yes ☐ No ☒
8. Only if you are asserting a wage loss claim, please state the following for EACH employer for the last seven (7) years:

Name of Employer	Address of Employer	Dates of Employment	Annual Gross Income	Your Position
		--/--/---- to --/--/---- <input type="checkbox"/> Present		

9. Have you ever been out of work for more than thirty (30) days for reasons related to your health in the last seven (7) years? Yes ☐ No ☒
10. If yes, please state the following:

Name of Employer	Dates	Health Reason
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

YOU MUST ATTACH TAX RETURNS, EMPLOYMENT AUTHORIZATIONS, AND IDENTIFY THE LOSS OF CONSORTIUM PLAINTIFF'S EMPLOYERS IF CLAIMING LOST WAGES OR LOST EARNING CAPACITY DAMAGES.

Worker's Compensation and Disability Claims

11. Within the last ten (10) years, have you ever filed for workers' compensation, social security, and/or state or federal disability benefits?
Yes ☐ No ☒
12. If yes, then as to EACH application, please state the following:

Year Claim Filed	Court	Nature of Claimed Injury	Period of Disability	Award Amount

Military Service

13. Have you ever served in any branch of the military? Yes ☐ No ☒
14. If yes, state the branch and dates of service:

Branch Name	Dates of Service
	--/--/---- to --/--/---- <input type="checkbox"/> Present

15. If yes, were you discharged for any reason relating to your health (whether physical, psychiatric, or other health condition)? Yes ☐ No ☐
16. If yes, state the condition:

Other Lawsuits

17. Within the last ten (10) years, have you filed a lawsuit, relating to any bodily injury, or made a claim, OTHER THAN the present suit? Yes ☐ No ☒

Computer Use

18. Apart from communications to or from your attorney, have you communicated via email, visited any chat rooms, or publicly posted a comment, message or blog entry on a public internet site regarding your experience with or injuries you attribute to Taxotere®, other chemotherapies, or alopecia/hair loss during the past ten (10) years? You should include all postings on public social network sites including Twitter, Facebook, MySpace, LinkedIn, or “blogs” that address the topics above.
Yes ☐ No ☒
19. If yes, please state the following:

Forum Name	Screen Name or User Handle	Date of Post	Substance of Post
		--/--/----	

20. Are you now or have you ever been a member of an alopecia support group?
Yes ☐ No ☒
- a) If yes, identify the group by name:
- b) When did you join the group?

III. PRODUCT IDENTIFICATION

**I HAVE RECORDS DEMONSTRATING USE OF TAXOTERE® OR OTHER
DOCETAXEL: Yes ☒ No ☐**

YOU MUST UPLOAD THEM BEFORE YOU SUBMIT THIS FACT SHEET

Taxotere®

1. Were you treated with brand name Taxotere®? Yes ☒ No ☐ Unknown ☐

Other Docetaxel

2. Were you treated with another Docetaxel or generic Taxotere®? Yes ☐ No ☒
3. If yes, select all that apply:

Name of Drug	Yes
Docetaxel – Sanofi-Aventis U.S. LLC d/b/a Winthrop US	<input type="checkbox"/>
Docetaxel – McKesson Corporation d/b/a McKesson Packaging	<input type="checkbox"/>
Docetaxel – Actavis LLC f/k/a Actavis Inc. / Actavis Pharma, Inc.	<input type="checkbox"/>
Docetaxel – Pfizer Inc.	<input type="checkbox"/>
Docetaxel – Sandoz Inc.	<input type="checkbox"/>
Docetaxel – Accord Healthcare, Inc.	<input type="checkbox"/>
Docetaxel – Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc. / Hospira, Inc.	<input type="checkbox"/>
Docetaxel – Sun Pharma Global FZE	<input type="checkbox"/>
Docetaxel – Sun Pharmaceutical Industries, Inc. f/k/a Caraco Pharmaceutical Laboratories, Ltd.	<input type="checkbox"/>
Docetaxel – Teva Parenteral Medicines, Inc.	<input type="checkbox"/>
Docetaxel – Dr. Reddy's Laboratories Limited	<input type="checkbox"/>
Docetaxel – Eagle Pharmaceuticals, Inc.	<input type="checkbox"/>
Docetaxel – Northstar Rx LLC	<input type="checkbox"/>
Docetaxel – Sagent Pharmaceuticals, Inc.	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

4. **IF YOU SELECTED “UNKNOWN” YOU MUST CERTIFY AS FOLLOWS:**

I certify that I have made reasonable, good faith efforts to identify the manufacturer of the Docetaxel used in my treatment, including requesting records from my infusion pharmacy, and the manufacturer either remains unknown at this time or I am awaiting the records:

☐

IV. MEDICAL INFORMATION

Vital Statistics

1. How old are you: [REDACTED]

2. Age at the time of your alleged injury: ■
3. Current weight: 224 lbs.
4. Current height:
Feet: 5 Inches: 11
5. Weight at time of alleged injury: 224

Gynecologic and Obstetric History

6. Have you ever been pregnant? Yes ☐ No ☒
 - a) Number of pregnancies:
 - b) Number of live births:
7. If you have children, please state the following for EACH child:

Child's Name	Address	Date of Birth
		--/--/----

8. Date of first period (menses): ■ Age: ■
9. Date of last period (menses): ■ Age: ■
10. Are you menopausal, perimenopausal or postmenopausal? Yes ☒ No ☐
11. For EACH year for the last seven (7) years before your first treatment with Taxotere® or Docetaxel and since then, who did you see for your annual gynecological exam? Also indicate whether an annual exam was skipped or missed.

Doctor	Office	Year	Skipped or Missed
Corsetti, Ralph L	1319 Jefferson Highway, New Orleans, LA 70121	2008	<input type="checkbox"/>
St. John, Fayne M	1221 South Clearview Parkway, Suite 100, Building A, New Orleans, LA 70121	2007	<input type="checkbox"/>
St. John, Fayne M	1221 South Clearview Parkway, Suite 100, Building A, New Orleans, LA 70121	2006	<input type="checkbox"/>
St. John, Fayne M	1221 South Clearview Parkway, Suite 100, Building A, New Orleans, LA 70121	2005	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara Street, Suite 500, New Orleans, LA 70115	2004	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara Street, Suite 500, New Orleans, LA 70115	2003	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara Street, Suite 500, New Orleans, LA 70115	2001	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara Street, Suite 500, New Orleans, LA 70115	2000	<input type="checkbox"/>

12. For EACH year after age 40, or before then if applicable, who did you see for your annual

mammogram? Also indicate whether an annual mammogram was skipped or missed.

Doctor	Office	Year	Skipped or Missed
Corsetti, Ralph L	Lieselotte Tansey Breast Center at Ochsner	2017	<input type="checkbox"/>
Corsetti, Ralph L	Lieselotte Tansey Breast Center at Ochsner	2016	<input type="checkbox"/>
Corsetti, Ralph L	Lieselotte Tansey Breast Center at Ochsner	2015	<input checked="" type="checkbox"/>
Corsetti, Ralph L	Lieselotte Tansey Breast Center at Ochsner, 1319 Jefferson Highway, New Orleans, LA 70121	2014	<input type="checkbox"/>
Corsetti, Ralph L	Lieselotte Tansey Breast Center at Ochsner	2013	<input type="checkbox"/>
Corsetti, Ralph L	Lieselotte Tansey Breast Center at Ochsner	2012	<input type="checkbox"/>
Corsetti, Ralph L	Lieselotte Tansey Breast Center at Ochsner	2011	<input type="checkbox"/>
Corsetti, Ralph L	Lieselotte Tansey Breast Center at Ochsner	2010	<input type="checkbox"/>
Corsetti, Ralph L	Lieselotte Tansey Breast Center at Ochsner	2009	<input type="checkbox"/>
Corsetti, Ralph L	Lieselotte Tansey Breast Center at Ochsner	2008	<input type="checkbox"/>
St. John, Fayne M	1221 South Clearview Parkway, Suite 100, Building A, New Orleans, LA 70121	2007	<input type="checkbox"/>
St. John, Fayne M	1221 South Clearview Parkway, Suite 100, Building A, New Orleans, LA 70121	2006	<input type="checkbox"/>
St. John, Fayne M	1221 South Clearview Parkway, Suite 100, Building A, New Orleans, LA 70121	2005	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara St #500, New Orleans, LA 70115	2004	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara St #500, New Orleans, LA 70115	2003	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara St #500, New Orleans, LA 70115	2002	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara St #500, New Orleans, LA 70115	2001	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara St #500, New Orleans, LA 70115	2000	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara St #500, New Orleans, LA 70115	1999	<input type="checkbox"/>
Gillespie, Veronica C	4429 Clara St #500, New Orleans, LA 70115	1998	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1997	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1996	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1995	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1994	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1993	<input type="checkbox"/>

Doctor	Office	Year	Skipped or Missed
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1992	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1991	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1990	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1989	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1988	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1987	<input type="checkbox"/>
	Touro Infirmary 1401 Foucher Street, New Orleans, Louisiana 70115	1986	<input type="checkbox"/>

Other Risk Factors

13. Have any family members been diagnosed with breast cancer?

Family Member	Diagnosed	Age at Diagnosis
	<input type="checkbox"/>	

14. Have you ever been diagnosed as having genes or gene mutations that carry an increased cancer risk (e.g., BRCA1, BRCA2)? Yes ☐ No ☒

a) If yes, which? N/A

15. Did you receive radiation treatments or exposure to radiation before the age of 30? Yes ☐ No ☒

a) If yes, describe the particulars of your treatment or exposure:

Tobacco Use History

For the ten (10) year period before your use of Taxotere® or Docetaxel up to the present, check the answer and fill in the blanks applicable to your history of tobacco use, including cigarettes, cigars, pipes, and/or chewing tobacco/snuff.

16. I currently use tobacco: Yes ☐ No ☒

17. I have never used tobacco: Yes ☒ No ☐

18. I used tobacco in the ten (10) years before Taxotere® or Docetaxel treatment:

Yes ☐ No ☒

19. Identify types of tobacco use:

Type	Used	Average Per Day	Duration of Use (Years)
Cigarettes	<input type="checkbox"/>		
Cigars	<input type="checkbox"/>		
Pipes	<input type="checkbox"/>		
Chewing tobacco/snuff	<input type="checkbox"/>		

Prescription Medications

20. Apart from chemotherapy, are there prescription or over-the-counter medications that you took on a regular basis or more than three (3) times in the seven (7) year period before you first took Taxotere®? Yes ☒ No ☐

For purposes of this question, “regular basis” means that you were directed by a healthcare provider to take a medication for at least forty-five (45) consecutive days.

21. If yes, please provide the following for EACH prescription medication:

Medication	Prescriber	Dates Taken
Synthroid	St. John, Fayne 1514 Jefferson Highway New Orleans, LA 70121	??/??/2007 to --/--/---- <input checked="" type="checkbox"/> Present
Synthroid	Andrews, Samuel 2700 Napoleon Avenue New Orleans, LA 70115	??/??/1995 to ??/??/2007 <input type="checkbox"/> Present

V. CANCER DIAGNOSIS AND TREATMENT

Cancer Diagnosis & Treatment Generally

1. Have you ever been diagnosed with cancer? Yes ☒ No ☐
2. Were you diagnosed with cancer more than once? Yes ☐ No ☒
3. Did you undergo any of the following for cancer?

Treatment	Treated
Surgery	<input checked="" type="checkbox"/>
Radiation	<input checked="" type="checkbox"/>

Treatment	Treated
Chemotherapy	<input checked="" type="checkbox"/>

4. For surgery, specify:

Type of Surgery	Treated
Double mastectomy	<input type="checkbox"/>
Left-side mastectomy	<input type="checkbox"/>
Right-side mastectomy	<input type="checkbox"/>
Lumpectomy	<input checked="" type="checkbox"/>
Other:	<input type="checkbox"/>

5. Please state the following for EACH cancer diagnosis:

Type of Cancer	Infiltrating Mucinous Carcinoma of the Breast
Date of Diagnosis	01/10/2008
Primary Oncologist	01/10/2008 to 08/6/2008 <input type="checkbox"/> Present Oncology Treatment/Chemotherapy Kardinal, Carl 115 Business Loop 70 West Columbia, MO 65203
Primary Oncologist	08/6/2008 to --/--/---- <input checked="" type="checkbox"/> Present Oncology Treatment Larned, Zoe 1514 Jefferson Highway, Suite 5 New Orleans, LA 70121
Primary Oncologist	01/10/2008 to --/--/---- <input checked="" type="checkbox"/> Present Oncology Treatment/Surgery Corsetti, Ralph 1319 Jefferson Highway New Orleans, LA 70121
Treatment Facility	01/10/2008 to --/--/---- <input checked="" type="checkbox"/> Present Oncology Treatment Lieselotte Tansey Breast Center at Ochsner 1319 Jefferson Highway New Orleans, LA 70121
Treatment Facility	01/10/2008 to --/--/---- <input checked="" type="checkbox"/> Present Oncology Treatment Ochsner Medical Center 1514 Jefferson Highway New Orleans, LA 70121
Treatment Facility	--/--/---- to --/--/---- <input type="checkbox"/> Present
Treatment Facility	--/--/---- to --/--/---- <input type="checkbox"/> Present

Particulars of Chemotherapy

6. When were you first diagnosed with the condition for which you were prescribed Taxotere® or Docetaxel? 01/10/2008
7. What was the diagnosis for which you were prescribed Taxotere® or Docetaxel?

Diagnosis	Diagnosed
Breast cancer	<input checked="" type="checkbox"/>
Non-small cell lung cancer	<input type="checkbox"/>
Prostate cancer	<input type="checkbox"/>
Gastric adenocarcinoma	<input type="checkbox"/>
Head and neck cancer	<input type="checkbox"/>
Other:	<input type="checkbox"/>

8. For breast cancer, specify:
- a) Tumor size:

Tumor Size	Yes
TX	<input type="checkbox"/>
T0	<input type="checkbox"/>
Tis	<input type="checkbox"/>
T1	<input type="checkbox"/>
T2	<input checked="" type="checkbox"/>
T3	<input type="checkbox"/>
T4 (T4a, T4b, T4c, T4d)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

- b) Metastasis: None (M0)
- c) Node involvement:

Node	Yes
Node + NX	<input type="checkbox"/>
Node + N0	<input checked="" type="checkbox"/>
Node + N1	<input type="checkbox"/>
Node + N2	<input type="checkbox"/>
Node + N3	<input type="checkbox"/>
Node – (negative)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

- d) HER2 + (positive): ☐ HER2- (negative): ☒ Unknown: ☐

- e) Estrogen receptor: Positive (ER+): ☒ Negative (ER-): ☐ Unknown: ☐
- f) Progesterone receptor: Positive (PR+): ☒ Negative (PR-): ☐ Unknown: ☐
9. Was Taxotere® or Docetaxel the only chemotherapy treatment that you ever received?
Yes ☐ No ☒ Unknown ☐
10. Have you ever been treated with other chemotherapy drugs, either alone or in combination with or sequentially with Taxotere® or Docetaxel? Yes ☒ No ☐ Unknown ☐
11. If yes, check which of the following chemotherapy drugs you took:

Drug	Yes
5-Fluorouracil (Eludex)	<input type="checkbox"/>
Actinomycin	<input type="checkbox"/>
Altretamine (Hexalen)	<input type="checkbox"/>
Amsacrine	<input type="checkbox"/>
Bleomycin	<input type="checkbox"/>
Busulfan (Busulfex, Myleran)	<input type="checkbox"/>
Cabazitaxel: Mitoxantrone	<input type="checkbox"/>
Carboplatin (Paraplatin)	<input type="checkbox"/>
Carmustine (BiCNU, Gliadel)	<input type="checkbox"/>
Cetuximab (Erbix)	<input type="checkbox"/>
Chlorambucil (Leukeran)	<input type="checkbox"/>
Cisplatin (Platinol)	<input type="checkbox"/>
Cyclophosphamide (Neosar)	<input checked="" type="checkbox"/>
Cytarabine (Depocyt)	<input type="checkbox"/>
Dacarbazine	<input type="checkbox"/>
Daunorubicin (Cerubidine, DaunoXome)	<input type="checkbox"/>
Doxorubicin (Adriamycin, Doxil)	<input checked="" type="checkbox"/>
Epirubicin (Ellence)	<input type="checkbox"/>
Erlotinib (Tarceva)	<input type="checkbox"/>
Etoposide (Etopophos, Toposar)	<input type="checkbox"/>
Everolimus (Afinitor, Zortress)	<input type="checkbox"/>
Faslodex (Fulvestrant)	<input type="checkbox"/>
Gemcitabine (Gemzar)	<input checked="" type="checkbox"/>
Hexamethylmelamine (Hexalen)	<input type="checkbox"/>
Hydroxyurea (Hydrea, Droxia)	<input type="checkbox"/>
Idarubicin (Idamycin)	<input type="checkbox"/>
Ifosfamide (Ifex)	<input type="checkbox"/>
L-asparaginase (crisantaspase)	<input type="checkbox"/>
Lomustine (Ceenu)	<input type="checkbox"/>

Drug	Yes
Melphalan (Alkeran)	<input type="checkbox"/>
Mercaptopurine (Purinethol, Purixan)	<input type="checkbox"/>
Methotrexate (Trexall, Rasuvo)	<input type="checkbox"/>
Mitomycin	<input type="checkbox"/>
Mitoxantrone	<input type="checkbox"/>
Nab-paclitaxel (Abraxane): Mitoxantrone	<input type="checkbox"/>
Nitrogen mustard	<input type="checkbox"/>
Paclitaxel (Taxol)	<input type="checkbox"/>
Panitumumab (Vectibix)	<input type="checkbox"/>
Procarbazine (Matulane)	<input type="checkbox"/>
Sorafenib (Nexavar)	<input type="checkbox"/>
Teniposide (Vumon)	<input type="checkbox"/>
Thioguanine (Tabloid)	<input type="checkbox"/>
Thiotepa (Tepadina)	<input type="checkbox"/>
Topotecan (Hycamtin)	<input type="checkbox"/>
Vemurafenib (Zelboraf)	<input type="checkbox"/>
Vinblastine	<input type="checkbox"/>
Vincristine (Mariqibo, Vincasar)	<input type="checkbox"/>
Vindesine	<input type="checkbox"/>
Vinorelbine (Alocrest, Navelbine)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

12. Please provide the following information regarding Taxotere® or Docetaxel:

- a) Number of cycles: 04
- b) Frequency: Every week ☐ Every three weeks ☒
- Other:
- c) First treatment date: 02/12/2008
- d) Last treatment date: 04/16/2008
- e) Dosage: 170 mg
- (1) Combined with another chemotherapy drug: ☒
- (2) Sequential with another chemotherapy drug: ☒
- (3) If so, describe the combination or sequence: Taxotere + Gemzar + Avastin x 4 cycles. Then, Adriamycin + Cytosan + Avastin x 4 cycles.

13. Prescribing Physician(s):

Prescribing Physician	Address
Kardinal, Carl	115 Business Loop 70 West Columbia, MO 65203

Prescribing Physician	Address
Larned, Zoe	1514 Jefferson Highway New Orleans, LA 70121

14. Treatment Facility:

Treatment Facility	Address
Ochsner Medical Center	1514 Jefferson Highway New Orleans, LA 70121

15. Identify EACH state where you resided when you began and while taking Taxotere® or Docetaxel:

State	From Date	To Date
LA	09/11/1946	--/--/---- <input checked="" type="checkbox"/> Present

16. Was your Taxotere® or Docetaxel treatment part of a clinical trial? Yes ☒ No ☐
Unknown ☐

17. If yes, please provide the name and location of the trial site:

a) Name of trial site: NSABP Trial B-40 (National Surgical Adjuvant Breast & Bowel Project)b) Location of trial site: <http://www.nsabp.pitt.edu/B-40.asp>**VI. CLAIM INFORMATION**

Current Status

1. Are you currently taking Taxotere® or Docetaxel? Yes ☐ No ☒
2. Are you currently cancer-free? Yes ☒ No ☐
3. If no, check those that apply to your CURRENT status:

Current Status	Yes
In remission	<input checked="" type="checkbox"/>
Currently receiving chemotherapy	<input type="checkbox"/>
Currently receiving radiation therapy	<input type="checkbox"/>
Currently hospitalized for cancer or cancer-related complications	<input type="checkbox"/>
Currently in home health or hospice care for cancer or cancer-related complications	<input type="checkbox"/>
Cancer returned after taking Taxotere® or Docetaxel	<input type="checkbox"/>

4. When was the last (most recent) date you consulted with an oncologist: 10/??/2016

Alleged Injury

5. State the injury you allege in this lawsuit and the dates between which you experienced the alleged injury. Check all that apply:

Alleged Injury	Yes	No	From	To
Persistent total alopecia – No hair growth on your head or body after six (6) months of discontinuing Taxotere® or Docetaxel treatment	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Persistent alopecia of your head – No hair growth on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment. Hair is present elsewhere on your body	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Hair Loss on Scalp	<input checked="" type="checkbox"/>	<input type="checkbox"/>	02/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Diffuse thinning of hair: partial scalp <input type="checkbox"/> Top <input type="checkbox"/> Sides <input type="checkbox"/> Back <input type="checkbox"/> Temples <input type="checkbox"/> Other:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Diffuse thinning of hair: total scalp <input checked="" type="checkbox"/> Top <input checked="" type="checkbox"/> Sides <input checked="" type="checkbox"/> Back <input checked="" type="checkbox"/> Temples <input type="checkbox"/> Other:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	02/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Significant thinning of the hair on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment – There are visible bald spots on your head no matter how you style your hair	<input checked="" type="checkbox"/>	<input type="checkbox"/>	02/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Moderate thinning of the hair on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment – There is noticeable hair loss but if you brush or style your hair, the hair loss is less evident	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Small bald area in the hair on your head	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Large bald area in the hair on your head	<input checked="" type="checkbox"/>	<input type="checkbox"/>	02/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Multiple bald spots in the hair on your head	<input checked="" type="checkbox"/>	<input type="checkbox"/>	02/??/2008	--/--/---- <input checked="" type="checkbox"/> Present

Alleged Injury	Yes	No	From	To
Change in the texture, thickness or color of your hair after Taxotere® or Docetaxel treatment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	02/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Other:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Eyebrows	<input checked="" type="checkbox"/>	<input type="checkbox"/>	02/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Permanent/Persistent Loss of Eyelashes	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Body Hair	<input checked="" type="checkbox"/>	<input type="checkbox"/>	02/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Permanent/Persistent Loss of Genital Hair	<input checked="" type="checkbox"/>	<input type="checkbox"/>	02/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Permanent/Persistent Loss of Nasal Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Ear Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Hair in Other Areas Describe:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present

6. Have you ever received treatment for the injury you allege in this lawsuit?

Yes ☒ No ☐

Name of Treating Physician	Dates of Treatment	Treatments
TOSTI, ANTONELLA	06/4/2018 to --/--/---- <input checked="" type="checkbox"/> Present	Initial visit on June 4, 2019. No records received yet.

7. Were you diagnosed by a healthcare provider for the injury you allege in this lawsuit?

Yes ☐ No ☒

Name of Diagnosing Physician	Dates of Treatment	Treatments
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

8. Have you discussed with any healthcare provider whether Taxotere® or Docetaxel caused or contributed to your alleged injury?

Yes ☐ No ☒

Name of Physician	Dates of Treatment	Treatments
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

Statement Information

9. Were you ever given any written instructions, including any prescriptions, packaging, package inserts, literature, medication guides, or dosing instructions, regarding chemotherapy, Taxotere® or Docetaxel? Yes ☒ No ☐

10. If yes, please describe the documents, if you no longer have them. If you have the documents, please produce them:

Description of Document	I Have the Documents	I Do Not Have the Documents
A clinical trial binder for note-keeping.	<input type="checkbox"/>	<input checked="" type="checkbox"/>

11. Were you given any oral instructions from a healthcare provider regarding chemotherapy or your use of Taxotere® or Docetaxel? Yes ☒ No ☐
12. If yes, please identify each healthcare provider who provided the oral instructions:

Name of Healthcare Provider
Cardinal, Carl G
Larned, Zoe

13. Have you ever seen any advertisements (e.g., in magazines or television commercials) for Taxotere® or Docetaxel? Yes ☐ No ☒
14. If yes, identify the advertisement or commercial, and approximately when you saw the advertisement or commercial:

Type of Advertisement or Commercial	Date of Advertisement or Commercial
	--/--/----

15. Other than through your attorneys, have you had any communication, oral or written, with any of the Defendants or their representatives? Yes ☐ No ☒
16. If yes, please identify:

Date of Communication	Method of Communication	Name of Representative	Substance of Communication
--/--/----			

17. Have you filed a MedWatch Adverse Event Report to the FDA? Yes ☐ No ☒

YOU MUST UPLOAD NOW ANY MEDICAL RECORDS IN YOUR POSSESSION DEMONSTRATING ALLEGED INJURY OR PHOTOGRAPHS SHOWING YOUR HAIR BEFORE AND AFTER TREATMENT WITH TAXOTERE® ALONG WITH THE DATE(S) THE PHOTOGRAPHS WERE TAKEN.

Other Claimed Damages

18. Mental or Emotional Damages: Do you claim that your use of Taxotere® or Docetaxel caused or aggravated any psychiatric or psychological condition? Yes ☐ No ☒
19. If yes, did you seek treatment for the psychiatric or psychological condition? Yes ☐ No ☐

Provider	Date	Condition
	--/------	

20. Medical Expenses: Do you claim that you incurred medical expenses for the alleged injury that you claim was caused by Taxotere® or Docetaxel? Yes ☐ No ☒
21. If yes, list all of your medical expenses, including amounts billed or paid by insurers and other third-party payors, which are related to any alleged injury you claim was caused by Taxotere® or Docetaxel:

Provider	Date	Expense
	--/------	

22. Lost Wages: Do you claim that you lost wages or suffered impairment of earning capacity because of the alleged injury that you claim was caused by Taxotere® or Docetaxel? Yes ☐ No ☒
23. If yes, state the annual gross income you earned for each of the three (3) years before the injury you claim was caused by Taxotere® or Docetaxel.

Year	Annual Gross Income

24. State the annual gross income for every year following the injury or condition you claim was caused by Taxotere® or Docetaxel.

Year	Annual Gross Income

25. Out-of-Pocket Expenses: Are you making a claim for lost out-of-pocket expenses? Yes ☒ No ☐
26. If yes, please identify and itemize all out-of-pocket expenses you have incurred:

Expense	Expense Amount
Wigs	\$45 per quarter

Expense	Expense Amount
Whole Foods Hair, Skin and Nail Vitamins	\$24.99 per month

VII. HAIR LOSS INFORMATION

Background

- Did you ever see a healthcare provider for hair loss BEFORE taking Taxotere® or Docetaxel?
Yes ☐ No ☒
- Did your hair loss begin during chemotherapy treatment? Yes ☒ No ☐
- If yes, did you FIRST experience hair loss:
 - After treatment with another chemotherapy agent: ☒
 - After treatment with Taxotere® or Docetaxel: ☒
- At any time before or during the hair loss were you:

Condition	Yes	Description
Pregnant	<input type="checkbox"/>	
Seriously ill	<input type="checkbox"/>	
Hospitalized	<input type="checkbox"/>	
Under severe stress	<input type="checkbox"/>	
Undergoing treatment for any other medical condition	<input checked="" type="checkbox"/>	Thyroid treatment with Synthroid.

- When did you FIRST discuss with or see a healthcare provider about your hair loss?
??/??/2008
- Have you started any special diets at any time before or during the hair loss?
Yes ☐ No ☒ Describe:

Hair Loss History

Question	No	Yes	Name of Healthcare Provider
Have you had a biopsy of your scalp to evaluate your hair loss problem?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Tosti, Antonella
Have you had blood tests done to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have your hormones ever been checked to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you ever been told by a doctor that you have a thyroid condition?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Andrews, Samuel S

Question	No	Yes	Name of Healthcare Provider
Have you ever been treated with thyroid hormone?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	St. John, Fayne M
Have you ever been told by a doctor that you have a low iron level?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

7. Have you ever been on endocrine or hormonal therapy, either before or after chemotherapy with Taxotere® or Docetaxel? Yes ☒ No ☐
8. If yes, please identify:

Treating Physician	Dates of Treatment	Treatment
Andrews, Samuel S	??/??/1995 to ??/??/2007 <input type="checkbox"/> Present	Synthroid
St. John, Fayne M	??/??/2007 to --/--/---- <input checked="" type="checkbox"/> Present	Synthroid
Larned, Zoe	??/??/2008 to --/--/---- <input checked="" type="checkbox"/> Present	Tamoxifen

9. Do you have any autoimmune diseases? Yes ☐ No ☒
10. If yes, check the following which describes you:

Autoimmune Disease	Yes
Lupus	<input type="checkbox"/>
Rheumatoid arthritis	<input type="checkbox"/>
Celiac disease	<input type="checkbox"/>
Type 1 diabetes	<input type="checkbox"/>
Sjogrens disease	<input type="checkbox"/>
Vitiligo	<input type="checkbox"/>
Hashimoto's	<input type="checkbox"/>
Other:	<input type="checkbox"/>

11. Were you taking any medications when your hair loss began? Yes ☒ No ☐

Medication
Taxotere
Gemzar
Avastin
Aloxi
Dexamethasone/Decadron

Benadryl
Synthroid

Hair Care

12. How often do you wash/shampoo your hair? Every 3 days

13. Check any of the following that apply to you currently or that have in the past:

Hair Treatment	Yes	Period of Time	Frequency
Hair chemically processed or straightened (relaxers, keratin, Brazilian blowout, Japanese straightening, other)	<input checked="" type="checkbox"/>	??/??/1990 to ??/??/2007 <input type="checkbox"/> Present	A few times a year
Hair heat processed or straightened (blow drying/ flat ironing, curling)	<input checked="" type="checkbox"/>	??/??/1985 to ??/??/2007 <input type="checkbox"/> Present	Once a week
Hair dyed	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Hair highlighted	<input checked="" type="checkbox"/>	??/??/1990 to ??/??/2007 <input type="checkbox"/> Present	
Braids	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Weaves	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Tight hairstyles (ponytails)	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Extensions	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Other:	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	

14. Have you ever used the following?

Hair Treatment	Yes
WEN Cleansing Conditioners	<input type="checkbox"/>
Unilever Suave Professionals Keratin Infusion	<input type="checkbox"/>
L'Oréal Chemical Relaxer	<input type="checkbox"/>

15. Has your hair care regimen been different in the past? Yes ☒ No ☐

a) If yes, describe: I used to go to the beauty salon every week to get hair done - shampoo, condition, blow dry & hot curl. Now, I only wash my head.

Hair Loss Treatment

16. Did you use any other methods to prevent hair loss during chemotherapy?

Hair Treatment	Yes
Folic Acid supplementation	<input type="checkbox"/>
Minoxidil	<input type="checkbox"/>
Other:	<input type="checkbox"/>

17. Did you wear a cool cap during chemotherapy treatment? Yes ☐ No ☒

18. If yes, which cooling cap did you wear:

19. Have you used any over-the-counter medications, supplements, or cosmetic aides for your hair loss? Yes ☒ No ☒

20. If yes, please state the following:

Treatment	When was it tried?	How long did you try it?	Did it help?
Over-the-counter vitamins for hair, nails, skin.	??/??/2008	2008 to Present	No

21. Has anything helped your hair loss? Yes ☐ No ☒

22. If yes, please specify:

Type of Product	Dates of Use	Place of Purchase	Results of Use
	--/--/---- to --/--/---- <input type="checkbox"/> Present		

23. As of the date you verify your PFS, how long have you had alopecia or incomplete hair regrowth? Late February, 2008 to Present

24. Has any hair regrowth occurred? Yes ☒ No ☐

25. Have you ever worn a wig to conceal your hair loss? Yes ☒ No ☐

26. Specify:

Dates Used	Period of Use	Place Purchased	Cost of Item
??/??/2008 to --/--/---- <input checked="" type="checkbox"/> Present	2008 to Present	Wig World. Various beauty supply stores.	\$45 every quarter

VIII. RECORD HOLDER IDENTIFICATION

Healthcare Providers:

1. Identify each physician, doctor, or other healthcare provider who has provided treatment to you for any reason in the past eight (8) years and the reason for consulting the healthcare

provider or mental healthcare provider.

YOU MUST INCLUDE YOUR ONCOLOGIST, RADIOLOGIST, DERMATOLOGIST, DERMATOLOGIST-PATHOLOGIST, HAIR LOSS SPECIALIST, GYNECOLOGIST, OBSTETRICIAN, AND PRIMARY CARE PHYSICIAN, ALONG WITH ANY OTHER HEALTHCARE PROVIDERS IDENTIFIED ABOVE

Name	Area or Specialty	Address	Dates	Reason for Consultation
Cardinal, Carl G	Oncology	115 Business Loop 70 West Columbia, MO 65203	01/10/2008 to 08/6/2008 <input type="checkbox"/> Present	Oncology/Breast Cancer Treatment
Larned, Zoe	Oncology	1514 Jefferson Highway, Suite 5 New Orleans, LA 70121	08/6/2008 to --/--/---- <input checked="" type="checkbox"/> Present	Oncology/Breast Cancer Treatment
Scroggins, Jr., Troy G	Radiation Oncology	1514 Jefferson Highway, Suite 7N New Orleans, LA 70121	01/10/2008 to ??/??/2010 <input type="checkbox"/> Present	Oncology Radiation Therapy
Theodossiou, Christos G	Oncology	1514 Jefferson Highway New Orleans, LA 70121	01/10/2008 to --/--/---- <input checked="" type="checkbox"/> Present	Oncology/Breast Cancer Treatment
Corsetti, Ralph	Oncology Surgery	1319 Jefferson Highway New Orleans, LA 70121	01/10/2008 to --/--/---- <input checked="" type="checkbox"/> Present	Oncology/Breast Cancer Surgery
St. John, Fayne M	Primary Care	1221 South Clearview Parkway New Orleans, LA 70121	??/??/2007 to --/--/---- <input checked="" type="checkbox"/> Present	Primary Care/ Thyroid
Andrews, Samuel A	Endocrinology/P rimary Care	2820 Napoleon Avenue New Orleans, LA 70115	??/??/1995 to ??/??/2007 <input type="checkbox"/> Present	Primary Care/ Thyroid
Gillespie, Veronica C	Ob-Gyn	4429 Clara Street, Suite 500 New Orleans, LA 70115	??/??/1999 to --/--/---- <input checked="" type="checkbox"/> Present	Ob-Gyn Care

Hospitals, Clinics, and Other Facilities:

- Identify each hospital, clinic, surgery center, physical therapy or rehabilitation center, or other healthcare facility where you have received inpatient or outpatient treatment (including emergency room treatment) in the past eight(8)years:

YOU MUST INCLUDE THE LOCATIONS FOR SURGERIES, RADIOLOGY, IMAGING, BIOPSIES, CHEMOTHERAPY, CHILD BIRTHS, GYNECOLOGIC PROCEDURES OR TREATMENT, ALONG WITH ANY OTHER HEALTHCARE FACILITIES

Name	Address	Dates	Reason for Treatment
Lieselotte Tansey Breast Center at Ochsner	1319 Jefferson Highway New Orleans, LA 70121	01/10/2008 to --/--/---- <input checked="" type="checkbox"/> Present	Breast Cancer Treatment
Ochsner Medical Center	1514 Jefferson Highway New Orleans, LA 70121	01/10/2008 to --/--/---- <input checked="" type="checkbox"/> Present	Breast Cancer Treatment
Ochsner Baptist Medical Center	2700 Napoleon Avenue New Orleans, LA 70115	01/1/2007 to --/--/---- <input checked="" type="checkbox"/> Present	Ob-Gyn Care
		--/--/---- to --/--/---- <input checked="" type="checkbox"/> Present	

Laboratories:

3. Identify each laboratory at which you had tests run in the past ten (10) years:

Name	Address	Dates	Test	Reason for Tests
Ochsner Medical Center	1514 Jefferson Highway New Orleans, LA 70121	01/1/2008 to --/--/---- <input checked="" type="checkbox"/> Present	Cancer Tests	Breast Cancer

Pharmacies:

4. To the best of your recollection, Identify each pharmacy, drugstore, and/or other supplier (including mail order) where you have had prescriptions filled or from which you have ever received any prescription medication within three (3) years prior to and three (3) years after your first treatment with Taxotere:

Name	Address	Dates	Medications
Walgreens	3216 Gentilly Boulevard New Orleans, LA 70122	01/1/1995 to --/--/---- <input checked="" type="checkbox"/> Present	Synthroid Tamoxifen

Retailers:

5. Identify each pharmacy, drugstore, and/or other retailer (including mail order) where you have purchased over-the-counter medications, or hair products in the past ten (10) years:

Name	Address	Dates	Purchases
N/A		--/--/---- to --/--/---- <input type="checkbox"/> Present	

Insurance Carriers:

6. Identify each health insurance carrier which provided you with medical coverage and/or pharmacy benefits for the last ten (10) years:

Carrier	Address	Name of Insured & SSN	Policy Number	Dates of Coverage
Blue Cross Blue Shield	P.O. Box 98029 Baton Rouge, LA 70898	Thibodeaux, Cynthia 439-72-6027		07/??/2015 to --/--/---- <input checked="" type="checkbox"/> Present
Medicare	7500 Security Boulevard Baltimore, MD 21244	Thibodeaux, Cynthia 439-72-6027		??/??/2012 to --/--/---- <input checked="" type="checkbox"/> Present
Humana/OHP	P.O. Box 14610 Lexington, KY 40512	Thibodeaux, Cynthia 439-72-6027		08/??/2007 to 07/??/2015 <input type="checkbox"/> Present

IX. DOCUMENT REQUESTS AND AUTHORIZATIONS

Please state which of the following documents you have in your possession. If you do not have the following documents but know they exist in the possession of others, state who has possession of the documents: Produce all documents in your possession (including writings on paper or in electronic form) and signed authorizations and attach a copy of them to this PFS.

Requests

Type of Document(s)	Yes	No	If No, who has the document(s)?
Documents you reviewed to prepare your answers to this Plaintiff Fact Sheet. <i>Your attorney may withhold some documents on claims of attorney-client privilege or work product protection and, if so, provide a privilege log</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Medical records or other documents related to the use of Taxotere® or Docetaxel at any time for the past twelve (12) years.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Medical records or other documents related to your treatment for any disease, condition or symptom referenced above for any time in the past twelve (12) years.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Laboratory reports and results of blood tests performed on you related to your hair loss.	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Pathology reports and results of biopsies performed on you related to your hair loss. <i>Plaintiffs or their counsel must maintain the slides and/or specimens requested in this subpart, or send a preservation notice, copying Defendants, to the healthcare facility where these items are maintained.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Dr. Antonella Tosti 1600 NW 10th Ave. RMSB -2023A Miami, FL 33136
Documents reflecting your use of any prescription drug or medication at any time within the past eight (8) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Pharmacy Providers
Documents identifying all chemotherapy agents that you have taken.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Documents for any workers' compensation, social security or other disability proceeding at any time within the last five (5) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Instructions, product warnings, package inserts, handouts or other materials that you were provided or obtained in connection with your use of Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Medical Providers
Advertisements or promotions for Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Articles discussing Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A

Type of Document(s)	Yes	No	If No, who has the document(s)?
Any packaging, container, box, or label for Taxotere® or Docetaxel that you were provided or obtained in connection with your use of Taxotere®. <i>Plaintiffs or their counsel must maintain the originals of these items.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Medical Providers
Documents which mention Taxotere® or Docetaxel or any alleged health risks related to Taxotere®. <i>Your attorney may withhold some legal documents, documents provided by your attorney, or documents obtained or created for the purpose of seeking legal advice or assistance on claims of attorney-client privilege or work product protection and, if so, provide a privilege log.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Medical Providers
Documents obtained directly or indirectly from any of the Defendants.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Communications or correspondence between you and any representative of the Defendants.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Photographs, drawing, slides, videos, recordings, DVDs, or any other media that show your alleged injury or its effect in your life.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Journals or diaries related to the use of Taxotere® or Docetaxel or your treatment for any disease, condition or symptom referenced above at any time for the past twelve (12) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A (Clinical Trial notebook was destroyed by flood in 2012).
Social media or internet posts to or through any site (including, but not limited to, Facebook, MySpace, LinkedIn, Google Plus, Windows Live, YouTube, Twitter, Instagram, Pinterest, blogs, and Internet chat rooms/message boards) relating to Taxotere® or Docetaxel or any of your claims in this lawsuit.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If you claim you have suffered a loss of earnings or earning capacity, your federal tax returns for each of the five (5) years preceding the injury you allege to be caused by Taxotere® or Docetaxel, and every year thereafter or W-2s for each of the five (5) years preceding the injury you allege to be caused by Taxotere® or Docetaxel, and every year thereafter.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If you claim any medical expenses, bills from any physician, hospital, pharmacy or other healthcare providers.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Records of any other expenses allegedly incurred as a result of your alleged injury.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If you are suing in a representative capacity, letters testamentary or letters of administration.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If you are suing in a representative capacity on behalf of a deceased person, decedent's death certificate and/or autopsy report.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A

Type of Document(s)	Yes	No	If No, who has the document(s)?
Photographs of you that are representative of your hair composition before treatment with Taxotere® or Docetaxel.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	see photos uploaded today 12.15.17
Photographs of you that are representative of your hair composition during treatment with Taxotere® or Docetaxel.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Photographs of you that are representative of your hair composition six months after conclusion of treatment with Taxotere® or Docetaxel.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Photographs of you that are representative of your hair composition in present day.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	see photos uploaded today 12.15.17
Signed authorizations for medical records related to any cancer treatment identified herein and all pharmacy records from three (3) years before and three (3) years after your first treatment with Taxotere in the forms attached hereto.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

X. DECLARATION

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that all of the information provided in connection with this Plaintiff Profile Form is true and correct to the best of my knowledge information and belief at the present time.

Signature		Date	
------------------	--	-------------	--

EXHIBIT Q

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL)
PRODUCTS LIABILITY
LITIGATION

MDL NO. 2740

SECTION "N" (5)

THIS DOCUMENT RELATES TO
ALL CASES

FIFTH AMENDED PLAINTIFF FACT SHEET

This Fact Sheet must be completed by each plaintiff who has filed a lawsuit related to the use of Taxotere® by the plaintiff or a plaintiff's decedent. Please answer every question to the best of your knowledge. In completing this Fact Sheet, you are under oath and must provide information that is true and correct to the best of your knowledge. If you cannot recall all of the details requested, please provide as much information as you can. You must supplement your responses if you learn that they are incomplete or incorrect in any material respect.

In filling out this form, please use the following definitions: (1) **"healthcare provider"** means any hospital, clinic, medical center, physician's office, infirmary, medical or diagnostic laboratory, or other facility that provides medical, dietary, psychiatric, or psychological care or advice, and any pharmacy, weight loss center, x-ray department, laboratory, physical therapist or physical therapy department, rehabilitation specialist, physician, psychiatrist, osteopath, homeopath, chiropractor, psychologist, nutritionist, dietician, or other persons or entities involved in the evaluation, diagnosis, care, and/or treatment of the plaintiff or plaintiff's decedent; (2) **"document"** means any writing or record of every type that is in your possession, including but not limited to written documents, documents in electronic format, cassettes, videotapes, photographs, charts, computer discs or tapes, and x-rays, drawings, graphs, phone-records, non-identical copies, and other data compilations from which information can be obtained and translated, if necessary, by the respondent through electronic devices into reasonably usable form.

Information provided by plaintiff will only be used for purposes related to this litigation and may be disclosed only as permitted by the protective order in this litigation. This Fact Sheet is completed pursuant to the Federal Rules of Civil Procedure governing discovery (or, for state court case, the governing rules of civil of the state in which the case is pending).

I. CORE CASE INFORMATION

Attorney Information

Please provide the following information for the civil action that you filed:

1. Caption: Sheila Crayton v. Sanofi, S.A., et. al.
2. Court and Docket No.: USDC EDLA 2:17-cv-05923
3. MDL Docket No. (if different): 2740

4. Date Lawsuit Filed: 06/19/17
5. Plaintiff's Attorney: Betsy Barnes
6. Plaintiff's Law Firm: Morris Bart, LLC
7. Attorney's Address: 601 Poydras St., 24th Fl.
New Orleans, LA 70130
8. Attorney's Phone Number: (504) 599-3234
9. Attorney's Email Address: bbarnes@morrisbart.com

Plaintiff Information

Please provide the following information for the individual on whose behalf this action was filed:

10. Name: CRAYTON, SHEILA
11. Street Address: [REDACTED]
12. City: [REDACTED]
13. State: [REDACTED]
14. Zip code: [REDACTED]
15. Date of Birth: [REDACTED]
16. Place of Birth: [REDACTED]
17. Social Security Number: [REDACTED]
18. Maiden or other names you have used or by which you have been known:
Gilmore
19. Sex: Male: ☐ Female: ☒
20. Race:

Race	Yes
American Indian or Alaska Native	<input type="checkbox"/>
Asian	<input type="checkbox"/>
Black or African American	<input checked="" type="checkbox"/>
Native Hawaiian or Other Pacific Islander	<input type="checkbox"/>
White	<input type="checkbox"/>

21. Ethnicity:

Ethnicity	Yes
Hispanic or Latino	<input type="checkbox"/>
Not Hispanic or Latino	<input checked="" type="checkbox"/>

22. Primary Language: English

Representative Information

If you are completing this questionnaire in a representative capacity (e.g., on behalf of the estate of a deceased person), please state the following:

23. Name:
24. Address:
25. Capacity in which you are representing the individual:
26. If you were appointed as a representative by a court, identify the State, Court and Case Number:
 - a) State:
 - b) Court:
 - c) Case Number:
27. Relationship to the Represented Person:
28. State the date of death of the decedent: --/--/----
29. State the place of death of the decedent:
30. Are you filling this questionnaire out on behalf of an individual who is deceased and on whom an autopsy was performed? Yes ☐ No ☐

If you are completing this questionnaire in a representative capacity, please respond to these questions with respect to the person whose medical treatment involved Taxotere® or Docetaxel.

II. PERSONAL INFORMATION

Relationship Information

Please provide the following information for the civil action that you filed:

1. Are you currently: Married: ☐ Single: ☒ Engaged: ☐
Significant other: ☐ Divorced: ☐ Widowed: ☒ Same sex partner: ☐
2. Have you ever been married? Yes ☒ No ☐
3. If yes, for EACH marriage, state the following:

Spouse's Name	Dates of Marriage	Date Marriage Ended	Nature of Termination
Crayton, Sr., Johnson L		12/25/2015	Legally Separated/Husband Deceased

Education

4. For each level of education you completed, please check below:
High School: ☒ Vocational School: ☐
College: AA: ☒ BA/BS: ☐ Masters: ☐ PhD: ☐ M.D.: ☐
Other:

Employment

5. Are you currently employed? Yes ☐ No ☒
6. If yes, state the following:
- a) Current employer name:
 - b) Address:
 - c) Telephone number:
 - d) Your position there:
7. Are you making a claim for lost wages or lost earning capacity?
Yes ☐ No ☒
8. Only if you are asserting a wage loss claim, please state the following for EACH employer for the last seven (7) years:

Name of Employer	Address of Employer	Dates of Employment	Annual Gross Income	Your Position
		--/--/---- to --/--/---- <input type="checkbox"/> Present		

9. Have you ever been out of work for more than thirty (30) days for reasons related to your health in the last seven (7) years? Yes ☐ No ☒
10. If yes, please state the following:

Name of Employer	Dates	Health Reason
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

YOU MUST ATTACH TAX RETURNS, EMPLOYMENT AUTHORIZATIONS, AND IDENTIFY THE LOSS OF CONSORTIUM PLAINTIFF'S EMPLOYERS IF CLAIMING LOST WAGES OR LOST EARNING CAPACITY DAMAGES.

Worker's Compensation and Disability Claims

11. Within the last ten (10) years, have you ever filed for workers' compensation, social security, and/or state or federal disability benefits?
Yes ☐ No ☒
12. If yes, then as to EACH application, please state the following:

Year Claim Filed	Court	Nature of Claimed Injury	Period of Disability	Award Amount

Military Service

13. Have you ever served in any branch of the military? Yes ☐ No ☒

14. If yes, state the branch and dates of service:

Branch Name	Dates of Service
	--/--/---- to --/--/---- <input type="checkbox"/> Present

15. If yes, were you discharged for any reason relating to your health (whether physical, psychiatric, or other health condition)? Yes ☐ No ☐

16. If yes, state the condition:

Other Lawsuits

17. Within the last ten (10) years, have you filed a lawsuit, relating to any bodily injury, or made a claim, OTHER THAN the present suit? Yes ☐ No ☒

Computer Use

18. Apart from communications to or from your attorney, have you communicated via email, visited any chat rooms, or publicly posted a comment, message or blog entry on a public internet site regarding your experience with or injuries you attribute to Taxotere®, other chemotherapies, or alopecia/hair loss during the past ten (10) years? You should include all postings on public social network sites including Twitter, Facebook, MySpace, LinkedIn, or “blogs” that address the topics above.

Yes ☐ No ☒

19. If yes, please state the following:

Forum Name	Screen Name or User Handle	Date of Post	Substance of Post
		--/--/----	

20. Are you now or have you ever been a member of an alopecia support group?

Yes ☐ No ☒

a) If yes, identify the group by name:

b) When did you join the group?

III. PRODUCT IDENTIFICATION

**I HAVE RECORDS DEMONSTRATING USE OF TAXOTERE ® OR OTHER
DOCETAXEL: Yes ☒ No ☐**

YOU MUST UPLOAD THEM BEFORE YOU SUBMIT THIS FACT SHEET

Taxotere®

1. Were you treated with brand name Taxotere ®? Yes ☒ No ☐ Unknown ☐

Other Docetaxel

2. Were you treated with another Docetaxel or generic Taxotere®? Yes ☐ No ☒
3. If yes, select all that apply:

Name of Drug	Yes
Docetaxel – Sanofi-Aventis U.S. LLC d/b/a Winthrop US	<input type="checkbox"/>
Docetaxel – McKesson Corporation d/b/a McKesson Packaging	<input type="checkbox"/>
Docetaxel – Actavis LLC f/k/a Actavis Inc. / Actavis Pharma, Inc.	<input type="checkbox"/>
Docetaxel – Pfizer Inc.	<input type="checkbox"/>
Docetaxel – Sandoz Inc.	<input type="checkbox"/>
Docetaxel – Accord Healthcare, Inc.	<input type="checkbox"/>
Docetaxel – Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc. / Hospira, Inc.	<input type="checkbox"/>
Docefrez – Sun Pharma Global FZE	<input type="checkbox"/>
Docefrez – Sun Pharmaceutical Industries, Inc. f/k/a Caraco Pharmaceutical Laboratories, Ltd.	<input type="checkbox"/>
Docetaxel – Teva Parenteral Medicines, Inc.	<input type="checkbox"/>
Docetaxel – Dr. Reddy’s Laboratories Limited	<input type="checkbox"/>
Docetaxel – Eagle Pharmaceuticals, Inc.	<input type="checkbox"/>
Docetaxel – Northstar Rx LLC	<input type="checkbox"/>
Docetaxel – Sagent Pharmaceuticals, Inc.	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

4. **IF YOU SELECTED “UNKNOWN” YOU MUST CERTIFY AS FOLLOWS:**

I certify that I have made reasonable, good faith efforts to identify the manufacturer of the Docetaxel used in my treatment, including requesting records from my infusion pharmacy, and the manufacturer either remains unknown at this time or I am awaiting the records: ☒

IV. MEDICAL INFORMATION

Vital Statistics

1. How old are you: ■■■■

2. Age at the time of your alleged injury: ■
3. Current weight: 165
4. Current height:
Feet: 5 Inches: 2
5. Weight at time of alleged injury: 166.3 lbs

Gynecologic and Obstetric History

6. Have you ever been pregnant? Yes ☒ No ☐
 - a) Number of pregnancies: 03
 - b) Number of live births: 03
7. If you have children, please state the following for EACH child:

Child's Name	Address	Date of Birth
Crayton, Jr., Johnson	2561 East Serene Street Las Vegas, NV 89174	■■■■
Crayton, Jyan L	8775 Sunny Side Drive LaPlace, LA 70068	■■■■
Fontenette, Tamela	Unknown New Orleans, LA ?????	■■■■

8. Date of first period (menses): ??/??/?? Age: ■
9. Date of last period (menses): ??/??/?? Age: ■
10. Are you menopausal, perimenopausal or postmenopausal? Yes ☒ No ☐
11. For EACH year for the last seven (7) years before your first treatment with Taxotere® or Docetaxel and since then, who did you see for your annual gynecological exam? Also indicate whether an annual exam was skipped or missed.

Doctor	Office	Year	Skipped or Missed
Blanton, Elizabeth N	2000-present The Women's Medical Center, 515 Westbank Expressway, Gretna, LA 70053	2000	<input type="checkbox"/>
Blanton, Elizabeth N	2000-present The Women's Medical Center, 515 Westbank Expressway, Gretna, LA 70053	2018	<input type="checkbox"/>

12. For EACH year after age 40, or before then if applicable, who did you see for your annual mammogram? Also indicate whether an annual mammogram was skipped or missed.

Doctor	Office	Year	Skipped or Missed
Blanton, Elizabeth N	1992-2007 The Women's Medical Center, 515 Westbank Expressway, Gretna, LA 70053	1992	<input type="checkbox"/>

Doctor	Office	Year	Skipped or Missed
Blanton, Elizabeth N	1992-2007 The Women's Medical Center, 515 Westbank Expressway, Gretna, LA 70053	2007	<input type="checkbox"/>
Blanton, Elizabeth N	2008-2018 Diagnostic Imaging Services 925 Avenue C. Marrero, LA 70072	2008	<input type="checkbox"/>
Blanton, Elizabeth N	2008-2018 Diagnostic Imaging Services 925 Avenue C. Marrero, LA 70072	2018	<input type="checkbox"/>
N			<input type="checkbox"/>
N			<input type="checkbox"/>
N			<input type="checkbox"/>

Other Risk Factors

13. Have any family members been diagnosed with breast cancer?

Family Member	Diagnosed	Age at Diagnosis
	<input type="checkbox"/>	

14. Have you ever been diagnosed as having genes or gene mutations that carry an increased cancer risk (e.g., BRCA1, BRCA2)? Yes ☐ No ☒

a) If yes, which?

15. Did you receive radiation treatments or exposure to radiation before the age of 30? Yes ☐ No ☒

a) If yes, describe the particulars of your treatment or exposure:

Tobacco Use History

For the ten (10) year period before your use of Taxotere® or Docetaxel up to the present, check the answer and fill in the blanks applicable to your history of tobacco use, including cigarettes, cigars, pipes, and/or chewing tobacco/snuff.

16. I currently use tobacco: Yes ☐ No ☒

17. I have never used tobacco: Yes ☒ No ☐

18. I used tobacco in the ten (10) years before Taxotere® or Docetaxel treatment:
Yes ☐ No ☒

19. Identify types of tobacco use:

Type	Used	Average Per Day	Duration of Use (Years)
Cigarettes	<input type="checkbox"/>		
Cigars	<input type="checkbox"/>		
Pipes	<input type="checkbox"/>		
Chewing tobacco/snuff	<input type="checkbox"/>		

Prescription Medications

20. Apart from chemotherapy, are there prescription or over-the-counter medications that you took on a regular basis or more than three (3) times in the seven (7) year period before you first took Taxotere®? Yes ☒ No ☐

For purposes of this question, “regular basis” means that you were directed by a healthcare provider to take a medication for at least forty-five (45) consecutive days.

21. If yes, please provide the following for EACH prescription medication:

Medication	Prescriber	Dates Taken
Verapamil	Rodriguez-Fierro, Carlos 1111 Medical Center Boulevard, Suite S350 Marrero, LA 70072	??/??/2005 to --/--/---- <input checked="" type="checkbox"/> Present
Nexium	Long, William 3909 Lapalco Boulevard, Suite 100 Harvey, LA 70058	??/??/2005 to --/--/---- <input checked="" type="checkbox"/> Present
Furosemide	Long, William 3909 Lapalco Boulevard, Suite 100 Harvey, LA 70058	01/1/2005 to --/--/---- <input checked="" type="checkbox"/> Present
Paxil	Blanton, Elizabeth 515 Westbank Expressway Gretna, LA 70053	??/??/2004 to --/--/---- <input checked="" type="checkbox"/> Present
Amitriptyline	Long, William 3909 Lapalco Boulevard, Suite 100 Harvey, LA 70058	??/??/2004 to --/--/---- <input checked="" type="checkbox"/> Present
Potassium	Long, William 3909 Lapalco Boulevard, Suite 100 Harvey, LA 70058	??/??/2005 to --/--/---- <input checked="" type="checkbox"/> Present

V. CANCER DIAGNOSIS AND TREATMENT

Cancer Diagnosis & Treatment Generally

1. Have you ever been diagnosed with cancer? Yes ☒ No ☐
2. Were you diagnosed with cancer more than once? Yes ☐ No ☒
3. Did you undergo any of the following for cancer?

Treatment	Treated
Surgery	<input checked="" type="checkbox"/>
Radiation	<input checked="" type="checkbox"/>
Chemotherapy	<input checked="" type="checkbox"/>

4. For surgery, specify:

Type of Surgery	Treated
Double mastectomy	<input type="checkbox"/>
Left-side mastectomy	<input checked="" type="checkbox"/>
Right-side mastectomy	<input type="checkbox"/>
Lumpectomy	<input type="checkbox"/>
Other:	<input type="checkbox"/>

5. Please state the following for EACH cancer diagnosis:

Type of Cancer	Breast Cancer
Date of Diagnosis	10/17/2007
Primary Oncologist	10/17/2007 to --/--/---- <input checked="" type="checkbox"/> Present Oncology/Chemotherapy Chandrasekaran, Nagarajan 120 Ochsner Blvd, Ste 380 Gretna, LA 70056
Primary Oncologist	10/17/2007 to --/--/---- <input checked="" type="checkbox"/> Present Oncology/Radiation Swanton, Robert 1120 Robert Boulevard, Suite 100 Slidell, LA 70458
Primary Oncologist	10/17/2007 to --/--/---- <input checked="" type="checkbox"/> Present Oncology/Surgery Kitahama, Akio 1111 Medical Center Boulevard, Suite 630 Marrero, LA 70072
Treatment Facility	10/17/2007 to --/--/---- <input checked="" type="checkbox"/> Present Oncology Treatment West Jefferson Medical Center 1101 Medical Center Boulevard Marrero, LA 70072
Treatment Facility	--/--/---- to --/--/---- <input type="checkbox"/> Present
Treatment Facility	--/--/---- to --/--/---- <input type="checkbox"/> Present
Treatment Facility	--/--/---- to --/--/---- <input type="checkbox"/> Present

Particulars of Chemotherapy

6. When were you first diagnosed with the condition for which you were prescribed Taxotere® or Docetaxel? 10/17/2007
7. What was the diagnosis for which you were prescribed Taxotere® or Docetaxel?

Diagnosis	Diagnosed
Breast cancer	<input checked="" type="checkbox"/>
Non-small cell lung cancer	<input type="checkbox"/>
Prostate cancer	<input type="checkbox"/>
Gastric adenocarcinoma	<input type="checkbox"/>
Head and neck cancer	<input type="checkbox"/>
Other:	<input type="checkbox"/>

8. For breast cancer, specify:
- a) Tumor size:

Tumor Size	Yes
TX	<input type="checkbox"/>
T0	<input type="checkbox"/>
Tis	<input type="checkbox"/>
T1	<input type="checkbox"/>
T2	<input checked="" type="checkbox"/>
T3	<input type="checkbox"/>
T4 (T4a, T4b, T4c, T4d)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

- b) Metastasis: M0 (No Distant Metastasis)
- c) Node involvement:

Node	Yes
Node + NX	<input type="checkbox"/>
Node + N0	<input checked="" type="checkbox"/>
Node + N1	<input type="checkbox"/>
Node + N2	<input type="checkbox"/>
Node + N3	<input type="checkbox"/>
Node – (negative)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

- d) HER2 + (positive): ☐ HER2- (negative): ☒ Unknown: ☐

- e) Estrogen receptor: Positive (ER+): ☐ Negative (ER-): ☒ Unknown: ☐
- f) Progesterone receptor: Positive (PR+): ☐ Negative (PR-): ☒ Unknown: ☐
9. Was Taxotere® or Docetaxel the only chemotherapy treatment that you ever received?
Yes ☐ No ☒ Unknown ☐
10. Have you ever been treated with other chemotherapy drugs, either alone or in combination with or sequentially with Taxotere® or Docetaxel? Yes ☒ No ☐ Unknown ☐
11. If yes, check which of the following chemotherapy drugs you took:

Drug	Yes
5-Fluorouracil (Eludex)	<input type="checkbox"/>
Actinomycin	<input type="checkbox"/>
Altretamine (Hexalen)	<input type="checkbox"/>
Amsacrine	<input type="checkbox"/>
Bleomycin	<input type="checkbox"/>
Busulfan (Busulfex, Myleran)	<input type="checkbox"/>
Cabazitaxel: Mitoxantrone	<input type="checkbox"/>
Carboplatin (Paraplatin)	<input type="checkbox"/>
Carmustine (BiCNU, Gliadel)	<input type="checkbox"/>
Cetuximab (Erbix)	<input type="checkbox"/>
Chlorambucil (Leukeran)	<input type="checkbox"/>
Cisplatin (Platinol)	<input type="checkbox"/>
Cyclophosphamide (Neosar)	<input checked="" type="checkbox"/>
Cytarabine (Depocyt)	<input type="checkbox"/>
Dacarbazine	<input type="checkbox"/>
Daunorubicin (Cerubidine, DaunoXome)	<input type="checkbox"/>
Doxorubicin (Adriamycin, Doxil)	<input checked="" type="checkbox"/>
Epirubicin (Ellence)	<input type="checkbox"/>
Erlotinib (Tarceva)	<input type="checkbox"/>
Etoposide (Etopophos, Toposar)	<input type="checkbox"/>
Everolimus (Afinitor, Zortress)	<input type="checkbox"/>
Faslodex (Fulvestrant)	<input type="checkbox"/>
Gemcitabine (Gemzar)	<input type="checkbox"/>
Hexamethylmelamine (Hexalen)	<input type="checkbox"/>
Hydroxyurea (Hydrea, Droxia)	<input type="checkbox"/>
Idarubicin (Idamycin)	<input type="checkbox"/>
Ifosfamide (Ifex)	<input type="checkbox"/>
L-asparaginase (crisantaspase)	<input type="checkbox"/>
Lomustine (Ceenu)	<input type="checkbox"/>

Drug	Yes
Melphalan (Alkeran)	<input type="checkbox"/>
Mercaptopurine (Purinethol, Purixan)	<input type="checkbox"/>
Methotrexate (Trexall, Rasuvo)	<input type="checkbox"/>
Mitomycin	<input type="checkbox"/>
Mitoxantrone	<input type="checkbox"/>
Nab-paclitaxel (Abraxane): Mitoxantrone	<input type="checkbox"/>
Nitrogen mustard	<input type="checkbox"/>
Paclitaxel (Taxol)	<input type="checkbox"/>
Panitumumab (Vectibix)	<input type="checkbox"/>
Procarbazine (Matulane)	<input type="checkbox"/>
Sorafenib (Nexavar)	<input type="checkbox"/>
Teniposide (Vumon)	<input type="checkbox"/>
Thioguanine (Tabloid)	<input type="checkbox"/>
Thiotepa (Tepadina)	<input type="checkbox"/>
Topotecan (Hycamtin)	<input type="checkbox"/>
Vemurafenib (Zelboraf)	<input type="checkbox"/>
Vinblastine	<input type="checkbox"/>
Vincristine (Mariqibo, Vincasar)	<input type="checkbox"/>
Vindesine	<input type="checkbox"/>
Vinorelbine (Alocrest, Navelbine)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

12. Please provide the following information regarding Taxotere® or Docetaxel:

a) Number of cycles: 04

b) Frequency: Every week ☐ Every three weeks ☒

Other:

c) First treatment date: 08/20/2008

d) Last treatment date: 10/22/2008

e) Dosage: 129.5-135mg

(1) Combined with another chemotherapy drug: ☐

(2) Sequential with another chemotherapy drug: ☒

(3) If so, describe the combination or sequence: Adriamycin + Cytosan, Followed by Taxotere

13. Prescribing Physician(s):

Prescribing Physician	Address
Chandrasekaran, Nagarajan	4513 Westbank Expressway Marrero, LA 70072

14. Treatment Facility:

Treatment Facility	Address
West Jefferson Medical Center	1101 Medical Center Boulevard Marrero, LA 70072

15. Identify EACH state where you resided when you began and while taking Taxotere® or Docetaxel:

State	From Date	To Date
LA	08/20/2008	10/22/2008 <input type="checkbox"/> Present

16. Was your Taxotere® or Docetaxel treatment part of a clinical trial? Yes ☐ No ☒ Unknown ☐

17. If yes, please provide the name and location of the trial site:

- Name of trial site:
- Location of trial site:

VI. CLAIM INFORMATION

Current Status

- Are you currently taking Taxotere® or Docetaxel? Yes ☐ No ☒
- Are you currently cancer-free? Yes ☒ No ☐
- If no, check those that apply to your CURRENT status:

Current Status	Yes
In remission	<input checked="" type="checkbox"/>
Currently receiving chemotherapy	<input type="checkbox"/>
Currently receiving radiation therapy	<input type="checkbox"/>
Currently hospitalized for cancer or cancer-related complications	<input type="checkbox"/>
Currently in home health or hospice care for cancer or cancer-related complications	<input type="checkbox"/>
Cancer returned after taking Taxotere® or Docetaxel	<input type="checkbox"/>

- When was the last (most recent) date you consulted with an oncologist: 04/??/2017

Alleged Injury

5. State the injury you allege in this lawsuit and the dates between which you experienced the alleged injury. Check all that apply:

Alleged Injury	Yes	No	From	To
Persistent total alopecia – No hair growth on your head or body after six (6) months of discontinuing Taxotere® or Docetaxel treatment	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Persistent alopecia of your head – No hair growth on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment. Hair is present elsewhere on your body	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Hair Loss on Scalp	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Diffuse thinning of hair: partial scalp <input checked="" type="checkbox"/> Top <input checked="" type="checkbox"/> Sides <input checked="" type="checkbox"/> Back <input checked="" type="checkbox"/> Temples <input type="checkbox"/> Other:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Diffuse thinning of hair: total scalp <input checked="" type="checkbox"/> Top <input checked="" type="checkbox"/> Sides <input checked="" type="checkbox"/> Back <input checked="" type="checkbox"/> Temples <input type="checkbox"/> Other:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Significant thinning of the hair on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment – There are visible bald spots on your head no matter how you style your hair	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Moderate thinning of the hair on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment – There is noticeable hair loss but if you brush or style your hair, the hair loss is less evident	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/2017 <input checked="" type="checkbox"/> Present
Small bald area in the hair on your head	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Large bald area in the hair on your head	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Multiple bald spots in the hair on your head	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Change in the texture, thickness or color of your hair after Taxotere® or Docetaxel treatment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Other:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present

Alleged Injury	Yes	No	From	To
Permanent/Persistent Loss of Eyebrows	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Permanent/Persistent Loss of Eyelashes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Permanent/Persistent Loss of Body Hair	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Permanent/Persistent Loss of Genital Hair	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present
Permanent/Persistent Loss of Nasal Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Ear Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Hair in Other Areas Describe: <u>Armpits and Legs</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2008	--/--/---- <input checked="" type="checkbox"/> Present

6. Have you ever received treatment for the injury you allege in this lawsuit?

Yes ☐ No ☒

Name of Treating Physician	Dates of Treatment	Treatments
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

7. Were you diagnosed by a healthcare provider for the injury you allege in this lawsuit?

Yes ☐ No ☒

Name of Diagnosing Physician	Dates of Treatment	Treatments
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

8. Have you discussed with any healthcare provider whether Taxotere® or Docetaxel caused or contributed to your alleged injury?

Yes ☐ No ☒

Name of Physician	Dates of Treatment	Treatments
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

Statement Information

9. Were you ever given any written instructions, including any prescriptions, packaging, package inserts, literature, medication guides, or dosing instructions, regarding chemotherapy, Taxotere® or Docetaxel? Yes ☒ No ☐

10. If yes, please describe the documents, if you no longer have them. If you have the documents, please produce them:

Description of Document	I Have the Documents	I Do Not Have the Documents
Chemotherapy Pamphlets	<input type="checkbox"/>	<input checked="" type="checkbox"/>

11. Were you given any oral instructions from a healthcare provider regarding chemotherapy or your use of Taxotere® or Docetaxel? Yes ☒ No ☐
12. If yes, please identify each healthcare provider who provided the oral instructions:

Name of Healthcare Provider
Chandrasekaran, Nagarajan

13. Have you ever seen any advertisements (e.g., in magazines or television commercials) for Taxotere® or Docetaxel? Yes ☐ No ☒
14. If yes, identify the advertisement or commercial, and approximately when you saw the advertisement or commercial:

Type of Advertisement or Commercial	Date of Advertisement or Commercial
	--/--/----

15. Other than through your attorneys, have you had any communication, oral or written, with any of the Defendants or their representatives? Yes ☐ No ☒
16. If yes, please identify:

Date of Communication	Method of Communication	Name of Representative	Substance of Communication
--/--/----			

17. Have you filed a MedWatch Adverse Event Report to the FDA? Yes ☐ No ☒

YOU MUST UPLOAD NOW ANY MEDICAL RECORDS IN YOUR POSSESSION DEMONSTRATING ALLEGED INJURY OR PHOTOGRAPHS SHOWING YOUR HAIR BEFORE AND AFTER TREATMENT WITH TAXOTERE® ALONG WITH THE DATE(S) THE PHOTOGRAPHS WERE TAKEN.

Other Claimed Damages

18. Mental or Emotional Damages: Do you claim that your use of Taxotere® or Docetaxel caused or aggravated any psychiatric or psychological condition? Yes ☒ No ☐
19. If yes, did you seek treatment for the psychiatric or psychological condition? Yes ☒ No ☐

Provider	Date	Condition
Long, William	01/1/2009	Depression
Blanton, Elizabeth N	12/31/2009	Depression

20. Medical Expenses: Do you claim that you incurred medical expenses for the alleged injury that you claim was caused by Taxotere® or Docetaxel? Yes ☐ No ☒
21. If yes, list all of your medical expenses, including amounts billed or paid by insurers and other third-party payors, which are related to any alleged injury you claim was caused by Taxotere® or Docetaxel:

Provider	Date	Expense
	--/------	

22. Lost Wages: Do you claim that you lost wages or suffered impairment of earning capacity because of the alleged injury that you claim was caused by Taxotere® or Docetaxel? Yes ☐ No ☒
23. If yes, state the annual gross income you earned for each of the three (3) years before the injury you claim was caused by Taxotere® or Docetaxel.

Year	Annual Gross Income

24. State the annual gross income for every year following the injury or condition you claim was caused by Taxotere® or Docetaxel.

Year	Annual Gross Income

25. Out-of-Pocket Expenses: Are you making a claim for lost out-of-pocket expenses? Yes ☒ No ☐
26. If yes, please identify and itemize all out-of-pocket expenses you have incurred:

Expense	Expense Amount
Wigs	\$130 Estimate
Lotions	\$30 Estimate
Hats	\$40 Estimate

VII. HAIR LOSS INFORMATION

Background

1. Did you ever see a healthcare provider for hair loss BEFORE taking Taxotere® or Docetaxel?
Yes ☐ No ☒
2. Did your hair loss begin during chemotherapy treatment? Yes ☒ No ☐
3. If yes, did you FIRST experience hair loss:
 - a) After treatment with another chemotherapy agent: ☐
 - b) After treatment with Taxotere® or Docetaxel: ☒
4. At any time before or during the hair loss were you:

Condition	Yes	Description
Pregnant	<input type="checkbox"/>	
Seriously ill	<input checked="" type="checkbox"/>	Lupus
Hospitalized	<input type="checkbox"/>	
Under severe stress	<input checked="" type="checkbox"/>	During Chemo
Undergoing treatment for any other medical condition	<input checked="" type="checkbox"/>	Lupus

5. When did you FIRST discuss with or see a healthcare provider about your hair loss?
--/--/----
6. Have you started any special diets at any time before or during the hair loss?
Yes ☒ No ☐ Describe: Lupus/Chemo

Hair Loss History

Question	No	Yes	Name of Healthcare Provider
Have you had a biopsy of your scalp to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you had blood tests done to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have your hormones ever been checked to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you ever been told by a doctor that you have a thyroid condition?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you ever been treated with thyroid hormone?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you ever been told by a doctor that you have a low iron level?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Long, William

7. Have you ever been on endocrine or hormonal therapy, either before or after chemotherapy with Taxotere® or Docetaxel? Yes ☐ No ☒
8. If yes, please identify:

Treating Physician	Dates of Treatment	Treatment
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

9. Do you have any autoimmune diseases? Yes ☒ No ☐
10. If yes, check the following which describes you:

Autoimmune Disease	Yes
Lupus	<input checked="" type="checkbox"/>
Rheumatoid arthritis	<input type="checkbox"/>
Celiac disease	<input type="checkbox"/>
Type 1 diabetes	<input type="checkbox"/>
Sjogrens disease	<input type="checkbox"/>
Vitiligo	<input type="checkbox"/>
Hashimoto's	<input type="checkbox"/>
Other:	<input type="checkbox"/>

11. Were you taking any medications when your hair loss began? Yes ☒ No ☐

Medication
Verapamil
Nexium
Furosemide
Paxil
Amitriptyline
Potassium

Hair Care

12. How often do you wash/shampoo your hair? Every 14 days
13. Check any of the following that apply to you currently or that have in the past:

Hair Treatment	Yes	Period of Time	Frequency
Hair chemically processed or straightened (relaxers, keratin, Brazilian blowout, Japanese straightening, other)	<input checked="" type="checkbox"/>	??/??/1996 to ??/??/2007 <input type="checkbox"/> Present	A few times a year
Hair heat processed or straightened (blow drying/ flat ironing, curling)	<input checked="" type="checkbox"/>	??/??/1998 to ??/??/2005 <input type="checkbox"/> Present	Once a month
Hair dyed	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Hair highlighted	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Braids	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Weaves	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Tight hairstyles (ponytails)	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Extensions	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Other:	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	

14. Have you ever used the following?

Hair Treatment	Yes
WEN Cleansing Conditioners	<input type="checkbox"/>
Unilever Suave Professionals Keratin Infusion	<input type="checkbox"/>
L'Oréal Chemical Relaxer	<input type="checkbox"/>

15. Has your hair care regimen been different in the past? Yes ☒ No ☐

a) If yes, describe: I have to use special conditioners. I wash my hair much less now that I don't have as much.

Hair Loss Treatment

16. Did you use any other methods to prevent hair loss during chemotherapy?

Hair Treatment	Yes
Folic Acid supplementation	<input type="checkbox"/>
Minoxidil	<input type="checkbox"/>
Other:	<input type="checkbox"/>

17. Did you wear a cool cap during chemotherapy treatment? Yes ☐ No ☒

18. If yes, which cooling cap did you wear:

19. Have you used any over-the-counter medications, supplements, or cosmetic aids for your hair loss? Yes ☒ No ☐

20. If yes, please state the following:

Treatment	When was it tried?	How long did you try it?	Did it help?
Vitamin E	??/??/2009	a few months	No

21. Has anything helped your hair loss? Yes ☐ No ☒

22. If yes, please specify:

Type of Product	Dates of Use	Place of Purchase	Results of Use
	--/--/---- to --/--/---- <input type="checkbox"/> Present		

23. As of the date you verify your PFS, how long have you had alopecia or incomplete hair regrowth? since chemotherapy

24. Has any hair regrowth occurred? Yes ☒ No ☐

25. Have you ever worn a wig to conceal your hair loss? Yes ☒ No ☐

26. Specify:

Dates Used	Period of Use	Place Purchased	Cost of Item
08/??/2008 to 06/??/2014 <input type="checkbox"/> Present	After Chemo	Marrero, LA	\$130 Estimate

VIII. RECORD HOLDER IDENTIFICATION

Healthcare Providers:

1. Identify each physician, doctor, or other healthcare provider who has provided treatment to you for any reason in the past eight (8) years and the reason for consulting the healthcare provider or mental healthcare provider.

YOU MUST INCLUDE YOUR ONCOLOGIST, RADIOLOGIST, DERMATOLOGIST, DERMATOLOGIST-PATHOLOGIST, HAIR LOSS SPECIALIST, GYNECOLOGIST, OBSTETRICIAN, AND PRIMARY CARE PHYSICIAN, ALONG WITH ANY OTHER HEALTHCARE PROVIDERS IDENTIFIED ABOVE

Name	Area or Specialty	Address	Dates	Reason for Consultation
Pounds, Jr., Jerry W	Rheumatology	2633 Napoleon Avenue, Suite 530 New Orleans, LA 70115	01/1/2015 to --/--/---- <input checked="" type="checkbox"/> Present	Lupus

Name	Area or Specialty	Address	Dates	Reason for Consultation
Sanders (Deceased), Reginald	Rheumatology	2633 Napoleon Avenue, Suite 530 New Orleans, LA 70115	01/1/2009 to 12/31/2015 <input type="checkbox"/> Present	Lupus
Rodriguez-Fierro, Carlos O	Cardiology	1111 Medical Center Boulevard, Suite S350 Marreo, LA 70072	01/1/2005 to --/--/---- <input checked="" type="checkbox"/> Present	Cardiology
Long, William	Primary Care	3909 Lapalco Boulevard, Suite 100 Harvey, LA 70058	01/1/2005 to --/--/---- <input checked="" type="checkbox"/> Present	Primary Care
Blanton, Elizabeth N	Ob-Gyn	515 Westbank Expressway Gretna, LA 70053	01/1/2000 to --/--/---- <input checked="" type="checkbox"/> Present	Ob-Gyn
Kitahama, Akio A	Oncology Surgeon	1111 Medical Center Boulevard, Suite 630 Marrero, LA 70072	10/17/2007 to --/--/---- <input checked="" type="checkbox"/> Present	Breast Cancer Surgery
Swanton, Robert	Oncology Radiation	1120 Robert Road Slidell, LA 70458	10/17/2007 to --/--/---- <input checked="" type="checkbox"/> Present	Breast Cancer Radiation
Chandrasekaren, Nagarajan	Oncology	120 Ochsner Blvd., Ste: 380 Gretna, LA 70056	10/17/2007 to --/--/---- <input type="checkbox"/> Present	Chemotherapy

Hospitals, Clinics, and Other Facilities:

- Identify each hospital, clinic, surgery center, physical therapy or rehabilitation center, or other healthcare facility where you have received inpatient or outpatient treatment (including emergency room treatment) in the past eight(8)years:

YOU MUST INCLUDE THE LOCATIONS FOR SURGERIES, RADIOLOGY, IMAGING, BIOPSIES, CHEMOTHERAPY, CHILD BIRTHS, GYNECOLOGIC PROCEDURES OR TREATMENT, ALONG WITH ANY OTHER HEALTHCARE FACILITIES

Name	Address	Dates	Reason for Treatment
West Jefferson Medical Center	1101 Medical Center Boulevard Marrero, LA 70072	10/17/2007 to --/--/---- <input checked="" type="checkbox"/> Present	Breast Cancer
The Women's Medical Center	515 Westbank Expressway Gretna, LA 70053	??/??/2000 to --/--/---- <input checked="" type="checkbox"/> Present	Ob-Gyn

Laboratories:

- Identify each laboratory at which you had tests run in the past ten (10) years:

Name	Address	Dates	Test	Reason for Tests
WEST JEFFERSON HOLDINGS, LLC	1101 Medical Center Blvd Marrero, LA 70072-3147	01/1/1999 to --/--/---- <input checked="" type="checkbox"/> Present	blood work	general healthcare

Pharmacies:

4. To the best of your recollection, Identify each pharmacy, drugstore, and/or other supplier (including mail order) where you have had prescriptions filled or from which you have ever received any prescription medication within three (3) years prior to and three (3) years after your first treatment with Taxotere:

Name	Address	Dates	Medications
Walgreens	1891 Barataria Boulevard Marrero, LA 70072	01/1/2005 to --/--/---- <input checked="" type="checkbox"/> Present	Verapamil, Nexium, Paxil, Amitriptyline, Potassium
Gem Drugs	139 Central Avenue Reserve, LA 70084	??/??/2014 to --/--/---- <input checked="" type="checkbox"/> Present	Furosemide

Retailers:

5. Identify each pharmacy, drugstore, and/or other retailer (including mail order) where you have purchased over-the-counter medications, or hair products in the past ten (10) years:

Name	Address	Dates	Purchases
Walgreens	1891 Barataria Boulevard Marrero, LA 70072	01/1/1999 to --/--/---- <input checked="" type="checkbox"/> Present	shampoo and conditioner

Insurance Carriers:

6. Identify each health insurance carrier which provided you with medical coverage and/or pharmacy benefits for the last ten (10) years:

Carrier	Address	Name of Insured & SSN	Policy Number	Dates of Coverage
Peoples Health - Medicare	3838 North Causeway Boulevard, Suite 2200 Metairie, LA 70002	Crayton, Sheila [REDACTED]	[REDACTED]	01/1/2007 to --/--/---- <input checked="" type="checkbox"/> Present

IX. DOCUMENT REQUESTS AND AUTHORIZATIONS

Please state which of the following documents you have in your possession. If you do not have the following documents but know they exist in the possession of others, state who has possession of the documents: Produce all documents in your possession (including writings on paper or in electronic form) and signed authorizations and attach a copy of them to this PFS.

Requests

Type of Document(s)	Yes	No	If No, who has the document(s)?
Documents you reviewed to prepare your answers to this Plaintiff Fact Sheet. <i>Your attorney may withhold some documents on claims of attorney-client privilege or work product protection and, if so, provide a privilege log</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Medical records or other documents related to the use of Taxotere® or Docetaxel at any time for the past twelve (12) years.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Medical records or other documents related to your treatment for any disease, condition or symptom referenced above for any time in the past twelve (12) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Medical Providers
Laboratory reports and results of blood tests performed on you related to your hair loss.	<input type="checkbox"/>	<input type="checkbox"/>	does not exist
Pathology reports and results of biopsies performed on you related to your hair loss. <i>Plaintiffs or their counsel must maintain the slides and/or specimens requested in this subpart, or send a preservation notice, copying Defendants, to the healthcare facility where these items are maintained.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Documents reflecting your use of any prescription drug or medication at any time within the past eight (8) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Pharmacy Providers
Documents identifying all chemotherapy agents that you have taken.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Medical Providers
Documents for any workers' compensation, social security or other disability proceeding at any time within the last five (5) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Instructions, product warnings, package inserts, handouts or other materials that you were provided or obtained in connection with your use of Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Advertisements or promotions for Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Articles discussing Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Any packaging, container, box, or label for Taxotere® or Docetaxel that you were provided or obtained in connection with your use of Taxotere®. <i>Plaintiffs or their counsel must maintain the originals of these items.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Documents which mention Taxotere® or Docetaxel or any alleged health risks related to Taxotere®. <i>Your attorney may withhold some legal documents, documents provided by your attorney, or documents obtained or created for the purpose of seeking legal advice or assistance on claims of attorney-client privilege or work product protection and, if so, provide a privilege log.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Documents obtained directly or indirectly from any of the Defendants.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A

Type of Document(s)	Yes	No	If No, who has the document(s)?
Communications or correspondence between you and any representative of the Defendants.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Photographs, drawing, slides, videos, recordings, DVDs, or any other media that show your alleged injury or its effect in your life.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Journals or diaries related to the use of Taxotere® or Docetaxel or your treatment for any disease, condition or symptom referenced above at any time for the past twelve (12) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Social media or internet posts to or through any site (including, but not limited to, Facebook, MySpace, LinkedIn, Google Plus, Windows Live, YouTube, Twitter, Instagram, Pinterest, blogs, and Internet chat rooms/message boards) relating to Taxotere® or Docetaxel or any of your claims in this lawsuit.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If you claim you have suffered a loss of earnings or earning capacity, your federal tax returns for each of the five (5) years preceding the injury you allege to be caused by Taxotere® or Docetaxel, and every year thereafter or W-2s for each of the five (5) years preceding the injury you allege to be caused by Taxotere® or Docetaxel, and every year thereafter.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If you claim any medical expenses, bills from any physician, hospital, pharmacy or other healthcare providers.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Records of any other expenses allegedly incurred as a result of your alleged injury.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Receipts Destroyed
If you are suing in a representative capacity, letters testamentary or letters of administration.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If you are suing in a representative capacity on behalf of a deceased person, decedent's death certificate and/or autopsy report.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Photographs of you that are representative of your hair composition before treatment with Taxotere® or Docetaxel.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Photographs of you that are representative of your hair composition during treatment with Taxotere® or Docetaxel.	<input type="checkbox"/>	<input type="checkbox"/>	does not exist
Photographs of you that are representative of your hair composition six months after conclusion of treatment with Taxotere® or Docetaxel.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Photographs of you that are representative of your hair composition in present day.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Signed authorizations for medical records related to any cancer treatment identified herein and all pharmacy records from three (3) years before and three (3) years after your first treatment with Taxotere in the forms attached hereto.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

X. DECLARATION

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that all of the information provided in connection with this Plaintiff Profile Form is true and correct to the best of my knowledge information and belief at the present time.

Signature		Date	
------------------	--	-------------	--

EXHIBIT R

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL)
PRODUCTS LIABILITY
LITIGATION

MDL NO. 2740

SECTION "H" (5)

THIS DOCUMENT RELATES TO
ALL CASES

THIRD AMENDED PLAINTIFF FACT SHEET

This Fact Sheet must be completed by each plaintiff who has filed a lawsuit related to the use of Taxotere® by the plaintiff or a plaintiff's decedent. Please answer every question to the best of your knowledge. In completing this Fact Sheet, you are under oath and must provide information that is true and correct to the best of your knowledge. If you cannot recall all of the details requested, please provide as much information as you can. You must supplement your responses if you learn that they are incomplete or incorrect in any material respect.

In filling out this form, please use the following definitions: (1) **"healthcare provider"** means any hospital, clinic, medical center, physician's office, infirmary, medical or diagnostic laboratory, or other facility that provides medical, dietary, psychiatric, or psychological care or advice, and any pharmacy, weight loss center, x-ray department, laboratory, physical therapist or physical therapy department, rehabilitation specialist, physician, psychiatrist, osteopath, homeopath, chiropractor, psychologist, nutritionist, dietician, or other persons or entities involved in the evaluation, diagnosis, care, and/or treatment of the plaintiff or plaintiff's decedent; (2) **"document"** means any writing or record of every type that is in your possession, including but not limited to written documents, documents in electronic format, cassettes, videotapes, photographs, charts, computer discs or tapes, and x-rays, drawings, graphs, phone-records, non-identical copies, and other data compilations from which information can be obtained and translated, if necessary, by the respondent through electronic devices into reasonably usable form.

Information provided by plaintiff will only be used for purposes related to this litigation and may be disclosed only as permitted by the protective order in this litigation. This Fact Sheet is completed pursuant to the Federal Rules of Civil Procedure governing discovery (or, for state court case, the governing rules of civil of the state in which the case is pending).

I. CORE CASE INFORMATION

Attorney Information

Please provide the following information for the civil action that you filed:

1. Caption: Stewart vs. Accord Healthcare, Inc., et al
2. Court and Docket No.: USDC EDLA 17-cv-10817
3. MDL Docket No. (if different):

4. Date Lawsuit Filed: 10/18/2017
5. Plaintiff's Attorney: Andrew Geiger/Allan Berger
6. Plaintiff's Law Firm: Allan Berger and Associates
7. Attorney's Address: 4173 Canal Street
New Orleans, LA 70119
8. Attorney's Phone Number: (504) 486-9481
9. Attorney's Email Address: aberger@allan-berger.com

Plaintiff Information

Please provide the following information for the individual on whose behalf this action was filed:

10. Name: STEWART, WANDA
11. Street Address: [REDACTED]
12. City: [REDACTED]ge
13. State: [REDACTED]
14. Zip code: [REDACTED]
15. Date of Birth: [REDACTED]
16. Place of Birth: [REDACTED]a
17. Social Security Number: [REDACTED]
18. Maiden or other names you have used or by which you have been known:
19. Sex: Male: ☐ Female: ☒
20. Race:

Race	Yes
American Indian or Alaska Native	<input type="checkbox"/>
Asian	<input type="checkbox"/>
Black or African American	<input checked="" type="checkbox"/>
Native Hawaiian or Other Pacific Islander	<input type="checkbox"/>
White	<input type="checkbox"/>

21. Ethnicity:

Ethnicity	Yes
Hispanic or Latino	<input type="checkbox"/>
Not Hispanic or Latino	<input checked="" type="checkbox"/>

22. Primary Language: English

Representative Information

If you are completing this questionnaire in a representative capacity (e.g., on behalf of the estate of a deceased person), please state the following:

23. Name:
24. Address:
25. Capacity in which you are representing the individual:
26. If you were appointed as a representative by a court, identify the State, Court and Case Number:
 - a) State:
 - b) Court:
 - c) Case Number:
27. Relationship to the Represented Person:
28. State the date of death of the decedent: --/--/----
29. State the place of death of the decedent:
30. Are you filling this questionnaire out on behalf of an individual who is deceased and on whom an autopsy was performed? Yes ☐ No ☒

If you are completing this questionnaire in a representative capacity, please respond to these questions with respect to the person whose medical treatment involved Taxotere® or Docetaxel.

II. PERSONAL INFORMATION

Relationship Information

Please provide the following information for the civil action that you filed:

1. Are you currently: Married: ☐ Single: ☒ Engaged: ☐
Significant other: ☐ Divorced: ☐ Widowed: ☐ Same sex partner: ☐
2. Have you ever been married? Yes ☐ No ☒
3. If yes, for EACH marriage, state the following:

Spouse's Name	Dates of Marriage	Date Marriage Ended	Nature of Termination
	--/--/----	--/--/----	

Education

4. For each level of education you completed, please check below:
High School: ☐ Vocational School: ☐
College: AA: ☐ BA/BS: ☐ Masters: ☒ PhD: ☐ M.D.: ☐
Other:

Employment

5. Are you currently employed? Yes ☒ No ☐
6. If yes, state the following:
- a) Current employer name: Department of Public Safety
 - b) Address: 7919 Independence Blvd
Baton Rouge, LA 70806
 - c) Telephone number: (225) 925-6006
 - d) Your position there: Human Resources Specialist
7. Are you making a claim for lost wages or lost earning capacity?
Yes ☐ No ☒
8. Only if you are asserting a wage loss claim, please state the following for EACH employer for the last seven (7) years:

Name of Employer	Address of Employer	Dates of Employment	Annual Gross Income	Your Position
		--/--/---- to --/--/---- <input type="checkbox"/> Present		

9. Have you ever been out of work for more than thirty (30) days for reasons related to your health in the last seven (7) years? Yes ☒ No ☐
10. If yes, please state the following:

Name of Employer	Dates	Health Reason
Louisiana Dept. of Public Safety	--/--/2012 to --/--/2012 <input type="checkbox"/> Present	Hysterectomy

YOU MUST ATTACH TAX RETURNS, EMPLOYMENT AUTHORIZATIONS, AND IDENTIFY THE LOSS OF CONSORTIUM PLAINTIFF'S EMPLOYERS IF CLAIMING LOST WAGES OR LOST EARNING CAPACITY DAMAGES.

Worker's Compensation and Disability Claims

11. Within the last ten (10) years, have you ever filed for workers' compensation, social security, and/or state or federal disability benefits?
Yes ☐ No ☒
12. If yes, then as to EACH application, please state the following:

Year Claim Filed	Court	Nature of Claimed Injury	Period of Disability	Award Amount

Military Service

13. Have you ever served in any branch of the military? Yes ☐ No ☒
14. If yes, state the branch and dates of service:

Branch Name	Dates of Service
	--/--/---- to --/--/---- <input type="checkbox"/> Present

15. If yes, were you discharged for any reason relating to your health (whether physical, psychiatric, or other health condition)? Yes ☐ No ☒
16. If yes, state the condition:

Other Lawsuits

17. Within the last ten (10) years, have you filed a lawsuit, relating to any bodily injury, or made a claim, OTHER THAN the present suit? Yes ☐ No ☒

Computer Use

18. Apart from communications to or from your attorney, have you communicated via email, visited any chat rooms, or publicly posted a comment, message or blog entry on a public internet site regarding your experience with or injuries you attribute to Taxotere®, other chemotherapies, or alopecia/hair loss during the past ten (10) years? You should include all postings on public social network sites including Twitter, Facebook, MySpace, LinkedIn, or “blogs” that address the topics above.
Yes ☐ No ☒
19. If yes, please state the following:

Forum Name	Screen Name or User Handle	Date of Post	Substance of Post
		--/--/----	

20. Are you now or have you ever been a member of an alopecia support group?
Yes ☐ No ☒
- a) If yes, identify the group by name:
- b) When did you join the group?

III. PRODUCT IDENTIFICATION

**I HAVE RECORDS DEMONSTRATING USE OF TAXOTERE ® OR OTHER
DOCETAXEL: Yes ☒ No ☐**

YOU MUST UPLOAD THEM BEFORE YOU SUBMIT THIS FACT SHEET

Taxotere®

1. Were you treated with brand name Taxotere ®? Yes ☐ No ☒ Unknown ☐

Other Docetaxel

2. Were you treated with another Docetaxel or generic Taxotere®? Yes ☒ No ☐
3. If yes, select all that apply:

Name of Drug	Yes
Docetaxel – Sanofi-Aventis U.S. LLC d/b/a Winthrop US	<input type="checkbox"/>
Docetaxel – McKesson Corporation d/b/a McKesson Packaging	<input type="checkbox"/>
Docetaxel – Actavis LLC f/k/a Actavis Inc. / Actavis Pharma, Inc.	<input type="checkbox"/>
Docetaxel – Pfizer Inc.	<input type="checkbox"/>
Docetaxel – Sandoz Inc.	<input checked="" type="checkbox"/>
Docetaxel – Accord Healthcare, Inc.	<input type="checkbox"/>
Docetaxel – Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc. / Hospira, Inc.	<input type="checkbox"/>
Docefrez – Sun Pharma Global FZE	<input type="checkbox"/>
Docefrez – Sun Pharmaceutical Industries, Inc. f/k/a Caraco Pharmaceutical Laboratories, Ltd.	<input type="checkbox"/>
Docetaxel – Teva Parenteral Medicines, Inc.	<input type="checkbox"/>
Docetaxel – Dr. Reddy’s Laboratories Limited	<input type="checkbox"/>
Docetaxel – Eagle Pharmaceuticals, Inc.	<input type="checkbox"/>
Docetaxel – Northstar Rx LLC	<input type="checkbox"/>
Docetaxel – Sagent Pharmaceuticals, Inc.	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

4. **IF YOU SELECTED “UNKNOWN” YOU MUST CERTIFY AS FOLLOWS:**

I certify that I have made reasonable, good faith efforts to identify the manufacturer of the Docetaxel used in my treatment, including requesting records from my infusion pharmacy, and the manufacturer either remains unknown at this time or I am awaiting the records: ☒

IV. MEDICAL INFORMATION

Vital Statistics

1. How old are you: [REDACTED]

2. Age at the time of your alleged injury: ■
3. Current weight: 178
4. Current height:
Feet: 5 Inches: 9
5. Weight at time of alleged injury: 203

Gynecologic and Obstetric History

6. Have you ever been pregnant? Yes ☒ No ☐
 - a) Number of pregnancies: 01
 - b) Number of live births:
7. If you have children, please state the following for EACH child:

Child's Name	Address	Date of Birth
No live births		--/--/----

8. Date of first period (menses): ■ Age: ■
9. Date of last period (menses): ■ Age: ■
10. Are you menopausal, perimenopausal or postmenopausal? Yes ☒ No ☐
11. For EACH year for the last seven (7) years before your first treatment with Taxotere® or Docetaxel and since then, who did you see for your annual gynecological exam? Also indicate whether an annual exam was skipped or missed.

Doctor	Office	Year	Skipped or Missed
		2007	<input checked="" type="checkbox"/>
		2008	<input checked="" type="checkbox"/>
		2009	<input checked="" type="checkbox"/>
		2010	<input checked="" type="checkbox"/>
Brown, Randall	La. Women's Healthcare 500 Rue de la vie, Suite 100, Baton Rouge, LA 70817	2011	<input type="checkbox"/>
Brown, Randall	La. Women's Healthcare 500 Rue de la vie, Suite 100, Baton Rouge, LA 70817	2012	<input type="checkbox"/>
		2013	<input checked="" type="checkbox"/>
		2014	<input checked="" type="checkbox"/>
		2015	<input checked="" type="checkbox"/>
		2016	<input checked="" type="checkbox"/>
Childress, Taylor	Baton Rouge Physicians 3401 No. Blvd., Ste. 100, Baton Rouge, La 70816	2017	<input type="checkbox"/>

12. For EACH year after age 40, or before then if applicable, who did you see for your annual mammogram? Also indicate whether an annual mammogram was skipped or missed.

Doctor	Office	Year	Skipped or Missed
		2008	<input checked="" type="checkbox"/>
		2009	<input checked="" type="checkbox"/>
		2010	<input checked="" type="checkbox"/>
Brown, Randall	La. Women's Healthcare 500 Rue de la vie, Suite 100, Baton Rouge, LA 70817	2011	<input type="checkbox"/>
Brown, Randall	La. Women's Healthcare 500 Rue de la vie, Suite 100, Baton Rouge, LA 70817	2012	<input type="checkbox"/>
Brown, Randall	La. Women's Healthcare 500 Rue de la vie, Suite 100, Baton Rouge, LA 70817	2013	<input type="checkbox"/>
	Double Mastectomy 2014	2014	<input type="checkbox"/>
	Double Mastectomy 2014	2015	<input type="checkbox"/>
	Double Mastectomy 2014	2016	<input type="checkbox"/>
	Double Mastectomy 2014	2017	<input type="checkbox"/>

Other Risk Factors

13. Have any family members been diagnosed with breast cancer?

Family Member	Diagnosed	Age at Diagnosis
	<input type="checkbox"/>	

14. Have you ever been diagnosed as having genes or gene mutations that carry an increased cancer risk (e.g., BRCA1, BRCA2)? Yes ☐ No ☒

a) If yes, which?

15. Did you receive radiation treatments or exposure to radiation before the age of 30? Yes ☐ No ☒

a) If yes, describe the particulars of your treatment or exposure:

Tobacco Use History

For the ten (10) year period before your use of Taxotere® or Docetaxel up to the present, check the answer and fill in the blanks applicable to your history of tobacco use, including cigarettes, cigars, pipes, and/or chewing tobacco/snuff.

16. I currently use tobacco: Yes ☐ No ☒

17. I have never used tobacco: Yes ☒ No ☐

18. I used tobacco in the ten (10) years before Taxotere® or Docetaxel treatment:
Yes ☐ No ☒

19. Identify types of tobacco use:

Type	Used	Average Per Day	Duration of Use (Years)
Cigarettes	<input type="checkbox"/>		
Cigars	<input type="checkbox"/>		
Pipes	<input type="checkbox"/>		
Chewing tobacco/snuff	<input type="checkbox"/>		

Prescription Medications

20. Apart from chemotherapy, are there prescription or over-the-counter medications that you took on a regular basis or more than three (3) times in the seven (7) year period before you first took Taxotere®? Yes ☐ No ☒

For purposes of this question, "regular basis" means that you were directed by a healthcare provider to take a medication for at least forty-five (45) consecutive days.

21. If yes, please provide the following for EACH prescription medication:

Medication	Prescriber	Dates Taken
N/A		--/--/---- to --/--/---- <input type="checkbox"/> Present

V. CANCER DIAGNOSIS AND TREATMENT

Cancer Diagnosis & Treatment Generally

1. Have you ever been diagnosed with cancer? Yes ☒ No ☐
2. Were you diagnosed with cancer more than once? Yes ☐ No ☒
3. Did you undergo any of the following for cancer?

Treatment	Treated
Surgery	<input checked="" type="checkbox"/>
Radiation	<input checked="" type="checkbox"/>
Chemotherapy	<input checked="" type="checkbox"/>

4. For surgery, specify:

Type of Surgery	Treated
Double mastectomy	<input checked="" type="checkbox"/>
Left-side mastectomy	<input type="checkbox"/>
Right-side mastectomy	<input type="checkbox"/>
Lumpectomy	<input type="checkbox"/>
Other:	<input type="checkbox"/>

5. Please state the following for EACH cancer diagnosis:

Type of Cancer	Breast Cancer
Date of Diagnosis	05/23/2014
Primary Oncologist	06/11/2014 to 10/15/2014 <input type="checkbox"/> Present Breast Cancer McCanless, Dr. Christopher 8595 Picardy Avenue #400 Baton Rouge, LA 70809
Primary Oncologist	--/--/---- to --/--/---- <input type="checkbox"/> Present
Primary Oncologist	--/--/---- to --/--/---- <input type="checkbox"/> Present
Treatment Facility	06/11/2014 to 10/15/2014 <input type="checkbox"/> Present Chemotherapy Hematology/Oncology 8595 Picardy Avenue #400 Baton Rouge, LA 70809
Treatment Facility	--/--/---- to --/--/---- <input type="checkbox"/> Present
Treatment Facility	--/--/---- to --/--/---- <input type="checkbox"/> Present
Treatment Facility	--/--/---- to --/--/---- <input type="checkbox"/> Present

Particulars of Chemotherapy

- When were you first diagnosed with the condition for which you were prescribed Taxotere® or Docetaxel? 05/23/2014
- What was the diagnosis for which you were prescribed Taxotere® or Docetaxel?

Diagnosis	Diagnosed
Breast cancer	<input checked="" type="checkbox"/>
Non-small cell lung cancer	<input type="checkbox"/>
Prostate cancer	<input type="checkbox"/>
Gastric adenocarcinoma	<input type="checkbox"/>
Head and neck cancer	<input type="checkbox"/>
Other:	<input type="checkbox"/>

8. For breast cancer, specify:

a) Tumor size:

Tumor Size	Yes
TX	<input type="checkbox"/>
T0	<input type="checkbox"/>
Tis	<input type="checkbox"/>
T1	<input checked="" type="checkbox"/>
T2	<input type="checkbox"/>
T3	<input type="checkbox"/>
T4 (T4a, T4b, T4c, T4d)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

b) Metastasis: Unknown

c) Node involvement:

Node	Yes
Node + NX	<input type="checkbox"/>
Node + N0	<input type="checkbox"/>
Node + N1	<input type="checkbox"/>
Node + N2	<input checked="" type="checkbox"/>
Node + N3	<input type="checkbox"/>
Node – (negative)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

d) HER2 + (positive): ☐ HER2- (negative): ☐ Unknown: ☒

e) Estrogen receptor: Positive (ER+): ☐ Negative (ER-): ☐ Unknown: ☒

f) Progesterone receptor: Positive (PR+): ☐ Negative (PR-): ☐ Unknown: ☒

9. Was Taxotere® or Docetaxel the only chemotherapy treatment that you ever received?

Yes ☐ No ☒ Unknown ☐

10. Have you ever been treated with other chemotherapy drugs, either alone or in combination with or sequentially with Taxotere® or Docetaxel? Yes ☒ No ☐ Unknown ☐

11. If yes, check which of the following chemotherapy drugs you took:

Drug	Yes
5-Fluorouracil (Eludex)	<input type="checkbox"/>
Actinomycin	<input type="checkbox"/>
Altretamine (Hexalen)	<input type="checkbox"/>
Amsacrine	<input type="checkbox"/>

Drug	Yes
Bleomycin	<input type="checkbox"/>
Busulfan (Busulfex, Myleran)	<input type="checkbox"/>
Cabazitaxel: Mitoxantrone	<input type="checkbox"/>
Carboplatin (Paraplatin)	<input type="checkbox"/>
Carmustine (BiCNU, Gliadel)	<input type="checkbox"/>
Cetuximab (Erbitux)	<input type="checkbox"/>
Chlorambucil (Leukeran)	<input type="checkbox"/>
Cisplatin (Platinol)	<input type="checkbox"/>
Cyclophosphamide (Neosar)	<input checked="" type="checkbox"/>
Cytarabine (Depocyt)	<input type="checkbox"/>
Dacarbazine	<input type="checkbox"/>
Daunorubicin (Cerubidine, DaunoXome)	<input type="checkbox"/>
Doxorubicin (Adriamycin, Doxil)	<input checked="" type="checkbox"/>
Epirubicin (Ellence)	<input type="checkbox"/>
Erlotinib (Tarceva)	<input type="checkbox"/>
Etoposide (Etopophos, Toposar)	<input type="checkbox"/>
Everolimus (Afinitor, Zortress)	<input type="checkbox"/>
Faslodex (Fulvestrant)	<input type="checkbox"/>
Gemcitabine (Gemzar)	<input type="checkbox"/>
Hexamethylmelamine (Hexalen)	<input type="checkbox"/>
Hydroxyurea (Hydrea, Droxia)	<input type="checkbox"/>
Idarubicin (Idamycin)	<input type="checkbox"/>
Ifosfamide (Ifex)	<input type="checkbox"/>
L-asparaginase (crisantaspase)	<input type="checkbox"/>
Lomustine (Ceenu)	<input type="checkbox"/>
Melphalan (Alkeran)	<input type="checkbox"/>
Mercaptopurine (Purinethol, Purixan)	<input type="checkbox"/>
Methotrexate (Trexall, Rasuvo)	<input type="checkbox"/>
Mitomycin	<input type="checkbox"/>
Mitoxantrone	<input type="checkbox"/>
Nab-paclitaxel (Abraxane): Mitoxantrone	<input type="checkbox"/>
Nitrogen mustard	<input type="checkbox"/>
Paclitaxel (Taxol)	<input type="checkbox"/>
Panitumumab (Vectibix)	<input type="checkbox"/>
Procarbazine (Matulane)	<input type="checkbox"/>
Sorafenib (Nexavar)	<input type="checkbox"/>
Teniposide (Vumon)	<input type="checkbox"/>

Drug	Yes
Thioguanine (Tabloid)	<input type="checkbox"/>
Thiotepa (Tepadina)	<input type="checkbox"/>
Topotecan (Hycamtin)	<input type="checkbox"/>
Vemurafenib (Zelboraf)	<input type="checkbox"/>
Vinblastine	<input type="checkbox"/>
Vincristine (Mariqibo, Vincasar)	<input type="checkbox"/>
Vindesine	<input type="checkbox"/>
Vinorelbine (Alocrest, Navelbine)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

12. Please provide the following information regarding Taxotere® or Docetaxel:

- a) Number of cycles: 06
- b) Frequency: Every week ☐ Every three weeks ☒
Other:
- c) First treatment date: 06/11/2014
- d) Last treatment date: 09/15/2014
- e) Dosage: 150 mg
- (1) Combined with another chemotherapy drug: ☒
- (2) Sequential with another chemotherapy drug: ☐
- (3) If so, describe the combination or sequence: Doxorubicin/Cytosan/Docetaxel

13. Prescribing Physician(s):

Prescribing Physician	Address
McCanless, Dr. Christopher	8595 Picardy Avenue #400 Baton Rouge, LA 70809

14. Treatment Facility:

Treatment Facility	Address
Hematology/Oncology Clinic	8595 Picardy Avenue #400 Baton Rouge, LA 70809

15. Identify EACH state where you resided when you began and while taking Taxotere® or Docetaxel:

State	From Date	To Date
LA	06/--/2014	--/--/---- <input checked="" type="checkbox"/> Present

16. Was your Taxotere® or Docetaxel treatment part of a clinical trial? Yes ☐ No ☒
Unknown ☐
17. If yes, please provide the name and location of the trial site:
- a) Name of trial site:
- b) Location of trial site:

VI. CLAIM INFORMATION

Current Status

1. Are you currently taking Taxotere® or Docetaxel? Yes ☐ No ☒
2. Are you currently cancer-free? Yes ☒ No ☐
3. If no, check those that apply to your CURRENT status:

Current Status	Yes
In remission	<input type="checkbox"/>
Currently receiving chemotherapy	<input type="checkbox"/>
Currently receiving radiation therapy	<input type="checkbox"/>
Currently hospitalized for cancer or cancer-related complications	<input type="checkbox"/>
Currently in home health or hospice care for cancer or cancer-related complications	<input type="checkbox"/>
Cancer returned after taking Taxotere® or Docetaxel	<input type="checkbox"/>

4. When was the last (most recent) date you consulted with an oncologist: 07/13/2017

Alleged Injury

5. State the injury you allege in this lawsuit and the dates between which you experienced the alleged injury. Check all that apply:

Alleged Injury	Yes	No	From	To
Persistent total alopecia – No hair growth on your head or body after six (6) months of discontinuing Taxotere® or Docetaxel treatment	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present

Alleged Injury	Yes	No	From	To
Persistent alopecia of your head – No hair growth on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment. Hair is present elsewhere on your body	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Hair Loss on Scalp	<input checked="" type="checkbox"/>	<input type="checkbox"/>	07/--/2014	--/--/---- <input checked="" type="checkbox"/> Present
Diffuse thinning of hair: partial scalp <input checked="" type="checkbox"/> Top <input checked="" type="checkbox"/> Sides <input checked="" type="checkbox"/> Back <input checked="" type="checkbox"/> Temples <input type="checkbox"/> Other:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	07/--/2014	--/--/---- <input checked="" type="checkbox"/> Present
Diffuse thinning of hair: total scalp <input type="checkbox"/> Top <input type="checkbox"/> Sides <input type="checkbox"/> Back <input type="checkbox"/> Temples <input type="checkbox"/> Other:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Significant thinning of the hair on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment – There are visible bald spots on your head no matter how you style your hair	<input checked="" type="checkbox"/>	<input type="checkbox"/>	07/--/2014	--/--/---- <input checked="" type="checkbox"/> Present
Moderate thinning of the hair on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment – There is noticeable hair loss but if you brush or style your hair, the hair loss is less evident	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Small bald area in the hair on your head	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Large bald area in the hair on your head	<input checked="" type="checkbox"/>	<input type="checkbox"/>	07/--/2014	--/--/---- <input checked="" type="checkbox"/> Present
Multiple bald spots in the hair on your head	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Change in the texture, thickness or color of your hair after Taxotere® or Docetaxel treatment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	07/--/2014	--/--/---- <input checked="" type="checkbox"/> Present
Other:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Eyebrows	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Eyelashes	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Body Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Genital Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Nasal Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Ear Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Hair in Other Areas Describe:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present

6. Have you ever received treatment for the injury you allege in this lawsuit?

Yes ☐ No ☒

Name of Treating Physician	Dates of Treatment	Treatments
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

7. Were you diagnosed by a healthcare provider for the injury you allege in this lawsuit?

Yes ☐ No ☒

Name of Diagnosing Physician	Dates of Treatment	Treatments
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

8. Have you discussed with any healthcare provider whether Taxotere® or Docetaxel caused or contributed to your alleged injury?

Yes ☐ No ☒

Name of Physician	Dates of Treatment	Treatments
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

Statement Information

9. Were you ever given any written instructions, including any prescriptions, packaging, package inserts, literature, medication guides, or dosing instructions, regarding chemotherapy, Taxotere® or Docetaxel? Yes ☒ No ☐
10. If yes, please describe the documents, if you no longer have them. If you have the documents, please produce them:

Description of Document	I Have the Documents	I Do Not Have the Documents
Coping with Cancer Printout	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Care during Chemotherapy and Beyond	<input type="checkbox"/>	<input checked="" type="checkbox"/>

11. Were you given any oral instructions from a healthcare provider regarding chemotherapy or your use of Taxotere® or Docetaxel? Yes ☐ No ☒
12. If yes, please identify each healthcare provider who provided the oral instructions:

Name of Healthcare Provider

13. Have you ever seen any advertisements (e.g., in magazines or television commercials) for Taxotere® or Docetaxel? Yes ☐ No ☒
14. If yes, identify the advertisement or commercial, and approximately when you saw the advertisement or commercial:

Type of Advertisement or Commercial	Date of Advertisement or Commercial
	--/--/----

15. Other than through your attorneys, have you had any communication, oral or written, with any of the Defendants or their representatives? Yes ☐ No ☒
16. If yes, please identify:

Date of Communication	Method of Communication	Name of Representative	Substance of Communication
--/--/----			

17. Have you filed a MedWatch Adverse Event Report to the FDA? Yes ☐ No ☒

YOU MUST UPLOAD NOW ANY MEDICAL RECORDS IN YOUR POSSESSION DEMONSTRATING ALLEGED INJURY OR PHOTOGRAPHS SHOWING YOUR HAIR BEFORE AND AFTER TREATMENT WITH TAXOTERE® ALONG WITH THE DATE(S) THE PHOTOGRAPHS WERE TAKEN.

Other Claimed Damages

18. Mental or Emotional Damages: Do you claim that your use of Taxotere® or Docetaxel caused or aggravated any psychiatric or psychological condition? Yes ☒ No ☐
19. If yes, did you seek treatment for the psychiatric or psychological condition? Yes ☐ No ☒

Provider	Date	Condition
	--/--/----	

20. Medical Expenses: Do you claim that you incurred medical expenses for the alleged injury that you claim was caused by Taxotere® or Docetaxel? Yes ☐ No ☒
21. If yes, list all of your medical expenses, including amounts billed or paid by insurers and other third-party payors, which are related to any alleged injury you claim was caused by Taxotere® or Docetaxel:

Provider	Date	Expense
	--/------	

22. Lost Wages: Do you claim that you lost wages or suffered impairment of earning capacity because of the alleged injury that you claim was caused by Taxotere® or Docetaxel?
Yes ☐ No ☒
23. If yes, state the annual gross income you earned for each of the three (3) years before the injury you claim was caused by Taxotere® or Docetaxel.

Year	Annual Gross Income

24. State the annual gross income for every year following the injury or condition you claim was caused by Taxotere® or Docetaxel.

Year	Annual Gross Income

25. Out-of-Pocket Expenses: Are you making a claim for lost out-of-pocket expenses?
Yes ☐ No ☒
26. If yes, please identify and itemize all out-of-pocket expenses you have incurred:

Expense	Expense Amount

VII. HAIR LOSS INFORMATION

Background

- Did you ever see a healthcare provider for hair loss BEFORE taking Taxotere® or Docetaxel?
Yes ☐ No ☒
- Did your hair loss begin during chemotherapy treatment? Yes ☒ No ☐
- If yes, did you FIRST experience hair loss:
 - After treatment with another chemotherapy agent: ☐
 - After treatment with Taxotere® or Docetaxel: ☒
- At any time before or during the hair loss were you:

Condition	Yes	Description
Pregnant	<input type="checkbox"/>	
Seriously ill	<input type="checkbox"/>	
Hospitalized	<input checked="" type="checkbox"/>	Hysterectomy 2012
Under severe stress	<input type="checkbox"/>	
Undergoing treatment for any other medical condition	<input type="checkbox"/>	

5. When did you FIRST discuss with or see a healthcare provider about your hair loss?
--/--/----
6. Have you started any special diets at any time before or during the hair loss?
Yes ☒ No ☐ Describe: Avoid spicy, fried, greasy foods, alcohol, foods high in acid content

Hair Loss History

Question	No	Yes	Name of Healthcare Provider
Have you had a biopsy of your scalp to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you had blood tests done to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have your hormones ever been checked to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you ever been told by a doctor that you have a thyroid condition?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you ever been treated with thyroid hormone?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you ever been told by a doctor that you have a low iron level?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

7. Have you ever been on endocrine or hormonal therapy, either before or after chemotherapy with Taxotere® or Docetaxel? Yes ☒ No ☐
8. If yes, please identify:

Treating Physician	Dates of Treatment	Treatment
Brown, Randall L	01/5/2012 to 10/3/2013 <input type="checkbox"/> Present	Hormone replacement for hot flashes

9. Do you have any autoimmune diseases? Yes ☐ No ☒
10. If yes, check the following which describes you:

Autoimmune Disease	Yes
Lupus	<input type="checkbox"/>
Rheumatoid arthritis	<input type="checkbox"/>
Celiac disease	<input type="checkbox"/>
Type 1 diabetes	<input type="checkbox"/>
Sjogrens disease	<input type="checkbox"/>
Vitiligo	<input type="checkbox"/>
Hashimoto's	<input type="checkbox"/>
Other:	<input type="checkbox"/>

11. Were you taking any medications when your hair loss began? Yes ☐ No ☒

Medication

Hair Care

12. How often do you wash/shampoo your hair? Every 7 days

13. Check any of the following that apply to you currently or that have in the past:

Hair Treatment	Yes	Period of Time	Frequency
Hair chemically processed or straightened (relaxers, keratin, Brazilian blowout, Japanese straightening, other)	<input checked="" type="checkbox"/>	09/1/1985 to 05/23/2014 <input type="checkbox"/> Present	A few times a year
Hair heat processed or straightened (blow drying/ flat ironing, curling)	<input checked="" type="checkbox"/>	09/25/1995 to 05/23/2014 <input type="checkbox"/> Present	2-3 times a week
Hair dyed	<input checked="" type="checkbox"/>	09/25/1995 to 05/23/2014 <input type="checkbox"/> Present	A few times a year
Hair highlighted	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Braids	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Weaves	<input checked="" type="checkbox"/>	09/25/1995 to 05/23/2014 <input type="checkbox"/> Present	A few times a year
Tight hairstyles (ponytails)	<input checked="" type="checkbox"/>	09/25/1995 to 05/23/2014 <input type="checkbox"/> Present	A few times a year
Extensions	<input checked="" type="checkbox"/>	09/23/1995 to 05/23/2014 <input type="checkbox"/> Present	A few times a year
Other:	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	

14. Have you ever used the following?

Hair Treatment	Yes
WEN Cleansing Conditioners	<input type="checkbox"/>
Unilever Suave Professionals Keratin Infusion	<input type="checkbox"/>
L'Oréal Chemical Relaxer	<input type="checkbox"/>

15. Has your hair care regimen been different in the past? Yes ☐ No ☒

a) If yes, describe:

Hair Loss Treatment

16. Did you use any other methods to prevent hair loss during chemotherapy?

Hair Treatment	Yes
Folic Acid supplementation	<input type="checkbox"/>
Minoxidil	<input type="checkbox"/>
Other:	<input type="checkbox"/>

17. Did you wear a cool cap during chemotherapy treatment? Yes ☐ No ☒

18. If yes, which cooling cap did you wear:

19. Have you used any over-the-counter medications, supplements, or cosmetic aides for your hair loss? Yes ☐ No ☒

20. If yes, please state the following:

Treatment	When was it tried?	How long did you try it?	Did it help?
	--/--/----		

21. Has anything helped your hair loss? Yes ☐ No ☒

22. If yes, please specify:

Type of Product	Dates of Use	Place of Purchase	Results of Use
	--/--/---- to --/--/---- <input type="checkbox"/> Present		

23. As of the date you verify your PFS, how long have you had alopecia or incomplete hair regrowth? since chemotherapy in 2014

24. Has any hair regrowth occurred? Yes ☐ No ☒

25. Have you ever worn a wig to conceal your hair loss? Yes ☒ No ☐

26. Specify:

Dates Used	Period of Use	Place Purchased	Cost of Item
07/7/2014 to --/--/---- <input checked="" type="checkbox"/> Present	Everyday	Divatress.com; Hair Crown Beauty Supply; Friday night Hair.com	\$274.00; \$49.00; \$50.00

VIII. RECORD HOLDER IDENTIFICATION

Healthcare Providers:

1. Identify each physician, doctor, or other healthcare provider who has provided treatment to you for any reason in the past eight (8) years and the reason for consulting the healthcare provider or mental healthcare provider.

YOU MUST INCLUDE YOUR ONCOLOGIST, RADIOLOGIST, DERMATOLOGIST, DERMATOLOGIST-PATHOLOGIST, HAIR LOSS SPECIALIST, GYNECOLOGIST, OBSTETRICIAN, AND PRIMARY CARE PHYSICIAN, ALONG WITH ANY OTHER HEALTHCARE PROVIDERS IDENTIFIED ABOVE

Name	Area or Specialty	Address	Dates	Reason for Consultation
McCanless, Christopher	Oncology	8595 Picardy Avenue #400 Baton Rouge, LA 70809	06/1/2014 to --/--/---- <input checked="" type="checkbox"/> Present	Breast Cancer
Shamlin, Kenyatta	Primary Care	8595 Picardy Avenue #400 Baton Rouge, LA 70809	10/3/2012 to --/--/---- <input checked="" type="checkbox"/> Present	Annual checkups
Childress, Taylor	Gyno	3401 North Blvd., Ste. 100 Baton Rouge, LA 70806	01/17/2017 to --/--/---- <input checked="" type="checkbox"/> Present	Annual check up
Bonner, Everett	Surgeon	7373 Perkins Road Baton Rouge, LA 70808	06/5/2014 to --/--/---- <input checked="" type="checkbox"/> Present	Breast Evaluation
Green, Garland	Cardiologist	8401 Picardy Ave Baton Rouge, LA 70809	05/27/2015 to --/--/---- <input checked="" type="checkbox"/> Present	chest x-rays
Theunissen, Taylor	Plastic Surgeon	5233 Dijon Drive Baton Rouge, LA 70806	03/9/2017 to --/--/---- <input checked="" type="checkbox"/> Present	Evaluation for reconstruction breast surgery
Russell, William	Radiation/Oncology	3401 North Blvd., #200 Baton Rouge, LA 70806	11/21/2014 to --/--/---- <input checked="" type="checkbox"/> Present	Evaluation before and after radiation treatment
Rheabottom, Tara	Dermo	10154 Jefferson Hwy Baton Rouge, LA 70819	11/11/2010 to --/--/---- <input checked="" type="checkbox"/> Present	Remove facial moles
Gawrenski, Dariusz	Neurologist	10101 Parkrow Avenue, Ste 200 Baton Rouge, LA 70810	01/13/2016 to 02/1/2016 <input type="checkbox"/> Present	Lab Tests, electrophoresis, serum protein
Kestler, Bruce	Dentist	554 Colonial Drive Baton Rouge, LA 70806	10/17/2016 to --/--/---- <input checked="" type="checkbox"/> Present	Oral evaluation
Thuy Nguyen	Dentist	2726 Continental Drive Baton Rouge, LA 70808	10/6/2016 to --/--/---- <input checked="" type="checkbox"/> Present	Evaluation for braces

Name	Area or Specialty	Address	Dates	Reason for Consultation
Detersan, Darryl	Ortho	8080 Blue Bonnet Blvd, Ste. 300 Baton Rouge, LA 70810	11/7/2016 to 01/9/2013 <input type="checkbox"/> Present	Shoulder pain issues
Messina, Lawrence	Bone and Joint	7301 Hennessy Blvd. Baton Rouge, LA 70808	02/11/2013 to 02/11/2013 <input type="checkbox"/> Present	Trigger finger pain
Walker, Paul	Urologist	8080 Blue Bonnet Blvd. Baton Rouge, LA 70810	11/29/2016 to 11/29/2016 <input type="checkbox"/> Present	Check bladder for cancer
Brown, Randall	Gyno	500 Rue Dela View Baton Rouge, LA 70817	11/--/2011 to 07/--/2005 <input type="checkbox"/> Present	Woman's health
Aucoin, Mark	Chiropractor	1857 Waddale Blvd. Baton Rouge, LA 70806	05/16/2012 to 05/16/2012 <input type="checkbox"/> Present	Evaluation neck and shoulder
Cavalier, Deborah	Pathologist	5339 Odonovan Drive Baton Rouge, LA 70808	05/23/2014 to 05/23/2014 <input type="checkbox"/> Present	Biopsy
Superneau, Duane	Genetics	8415 Goodwood Blvd. Baton Rouge, LA 70808	01/8/2015 to 01/8/2015 <input type="checkbox"/> Present	Genetic testing

Hospitals, Clinics, and Other Facilities:

- Identify each hospital, clinic, surgery center, physical therapy or rehabilitation center, or other healthcare facility where you have received inpatient or outpatient treatment (including emergency room treatment) in the past eight(8)years:

YOU MUST INCLUDE THE LOCATIONS FOR SURGERIES, RADIOLOGY, IMAGING, BIOPSIES, CHEMOTHERAPY, CHILD BIRTHS, GYNECOLOGIC PROCEDURES OR TREATMENT, ALONG WITH ANY OTHER HEALTHCARE FACILITIES

Name	Address	Dates	Reason for Treatment
Hematology/Oncology	8595 Picardy Ave., #400 Baton Rouge, LA 70809	06/11/2014 to 10/15/2014 <input type="checkbox"/> Present	Chemotherapy
Woman's Hospital	100 Woman's Way Baton Rouge, LA 70817	01/3/2012 to --/--/---- <input checked="" type="checkbox"/> Present	Hysterectomy; Reconstruction surgery; Biopsy
Baton Rouge General	8585 Picardy Avenue Baton Rouge, LA 70809	11/7/2014 to --/--/---- <input checked="" type="checkbox"/> Present	Port surgery, radiology, mastectomy

Laboratories:

- Identify each laboratory at which you had tests run in the past ten (10) years:

Name	Address	Dates	Test	Reason for Tests
United Technology LLC	7855 Howell Blvd. Baton Rouge, LA 70807	11/7/2012 to 11/7/2012 <input type="checkbox"/> Present	Urine Test	New patients check up

Name	Address	Dates	Test	Reason for Tests
Cardiovascular Institute	8401 Picardy Avenue Baton Rouge, LA 70809	05/29/2015 to 05/29/2015 <input type="checkbox"/> Present	EKG, Lipid test	Heart check up

Pharmacies:

4. To the best of your recollection, Identify each pharmacy, drugstore, and/or other supplier (including mail order) where you have had prescriptions filled or from which you have ever received any prescription medication within three (3) years prior to and three (3) years after your first treatment with Taxotere:

Name	Address	Dates	Medications
Walgreens	9820 Old Hammond Hwy Baton Rouge, LA 70816	06/6/2016 to --/--/---- <input checked="" type="checkbox"/> Present	Diazepan, Atavistatin, hydrocodone;
Walgreens	5061 Main Street Zachary, LA 70791	01/5/2012 to 11/30/2012 <input type="checkbox"/> Present	hydrocodone, amoxicillin; HRT
Walmart	5801 Main Street Zachary, LA 70791	01/9/2012 to 11/30/2012 <input type="checkbox"/> Present	HRT
Woman Hospital Pharmacy	100 Women"s Way Baton Rouge, LA 70817	05/1/2017 to 05/1/2017 <input type="checkbox"/> Present	Cephalexin
Hematology Oncology Clinic	8595 Picardy avenue Baton Rouge, LA 70809	06/6/2014 to 09/24/2014 <input type="checkbox"/> Present	Ondansertron, prochlorperzine

Retailers:

5. Identify each pharmacy, drugstore, and/or other retailer (including mail order) where you have purchased over-the-counter medications, or hair products in the past ten (10) years:

Name	Address	Dates	Purchases
Walgreens	9820 Old Hammand Hwy Baton Rouge, LA 70816	12/1/2012 to --/--/---- <input checked="" type="checkbox"/> Present	Vitamins, tylenol, magnesium, shampoo/conditioners
Walmart	5801 Main Street Zachery, LA 70791	10/1/2010 to 01/30/2012 <input type="checkbox"/> Present	Vitamins, sinus medicine, hairgels, shampoo/conditioners
Rite Aid	7570 Jefferson Hwy Baton Rouge, LA 70806	12/1/2012 to --/--/---- <input checked="" type="checkbox"/> Present	Advil, Vitamins, sinus medications, shampoo/conditioners, hairspray
Hair Crown	9615 Airline Hwy Baton Rouge, LA 70501	06/2/2014 to --/--/---- <input checked="" type="checkbox"/> Present	hair spray, gels, shampoo/conditioner

Insurance Carriers:

6. Identify each health insurance carrier which provided you with medical coverage and/or pharmacy benefits for the last ten (10) years:

Carrier	Address	Name of Insured & SSN	Policy Number	Dates of Coverage
Blue Cross/Blue Shield	5525 Reitz Avenue Baton Rouge, LA 70809	Stewart, Wanda J [REDACTED]	[REDACTED]	--/--/2007 to --/--/---- <input checked="" type="checkbox"/> Present

IX. DOCUMENT REQUESTS AND AUTHORIZATIONS

Please state which of the following documents you have in your possession. If you do not have the following documents but know they exist in the possession of others, state who has possession of the documents: Produce all documents in your possession (including writings on paper or in electronic form) and signed authorizations and attach a copy of them to this PFS.

Requests

Type of Document(s)	Yes	No	If No, who has the document(s)?
Documents you reviewed to prepare your answers to this Plaintiff Fact Sheet. <i>Your attorney may withhold some documents on claims of attorney-client privilege or work product protection and, if so, provide a privilege log</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Medical records or other documents related to the use of Taxotere® or Docetaxel at any time for the past twelve (12) years.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Medical records or other documents related to your treatment for any disease, condition or symptom referenced above for any time in the past twelve (12) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Treating physicians
Laboratory reports and results of blood tests performed on you related to your hair loss.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pathology reports and results of biopsies performed on you related to your hair loss. <i>Plaintiffs or their counsel must maintain the slides and/or specimens requested in this subpart, or send a preservation notice, copying Defendants, to the healthcare facility where these items are maintained.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Documents reflecting your use of any prescription drug or medication at any time within the past eight (8) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Pharmacy records
Documents identifying all chemotherapy agents that you have taken.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Type of Document(s)	Yes	No	If No, who has the document(s)?
Documents for any workers' compensation, social security or other disability proceeding at any time within the last five (5) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Unknown
Instructions, product warnings, package inserts, handouts or other materials that you were provided or obtained in connection with your use of Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Unknown
Advertisements or promotions for Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Unknown
Articles discussing Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Unknown
Any packaging, container, box, or label for Taxotere® or Docetaxel that you were provided or obtained in connection with your use of Taxotere®. <i>Plaintiffs or their counsel must maintain the originals of these items.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Unknown
Documents which mention Taxotere® or Docetaxel or any alleged health risks related to Taxotere®. <i>Your attorney may withhold some legal documents, documents provided by your attorney, or documents obtained or created for the purpose of seeking legal advice or assistance on claims of attorney-client privilege or work product protection and, if so, provide a privilege log.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Unknown
Documents obtained directly or indirectly from any of the Defendants.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Communications or correspondence between you and any representative of the Defendants.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Photographs, drawing, slides, videos, recordings, DVDs, or any other media that show your alleged injury or its effect in your life.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Photos of hair were provided
Journals or diaries related to the use of Taxotere® or Docetaxel or your treatment for any disease, condition or symptom referenced above at any time for the past twelve (12) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Social media or internet posts to or through any site (including, but not limited to, Facebook, MySpace, LinkedIn, Google Plus, Windows Live, YouTube, Twitter, Instagram, Pinterest, blogs, and Internet chat rooms/message boards) relating to Taxotere® or Docetaxel or any of your claims in this lawsuit.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If you claim you have suffered a loss of earnings or earning capacity, your federal tax returns for each of the five (5) years preceding the injury you allege to be caused by Taxotere® or Docetaxel, and every year thereafter or W-2s for each of the five (5) years preceding the injury you allege to be caused by Taxotere® or Docetaxel, and every year thereafter.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If you claim any medical expenses, bills from any physician, hospital, pharmacy or other healthcare providers.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Providers

Type of Document(s)	Yes	No	If No, who has the document(s)?
Records of any other expenses allegedly incurred as a result of your alleged injury.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Providers
If you are suing in a representative capacity, letters testamentary or letters of administration.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If you are suing in a representative capacity on behalf of a deceased person, decedent's death certificate and/or autopsy report.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Photographs of you that are representative of your hair composition before treatment with Taxotere® or Docetaxel.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Photographs of you that are representative of your hair composition during treatment with Taxotere® or Docetaxel.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Photographs of you that are representative of your hair composition six months after conclusion of treatment with Taxotere® or Docetaxel.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Photographs of you that are representative of your hair composition in present day.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Signed authorizations for medical records related to any cancer treatment identified herein and all pharmacy records from three (3) years before and three (3) years after your first treatment with Taxotere in the forms attached hereto.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

X. DECLARATION

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that all of the information provided in connection with this Plaintiff Profile Form is true and correct to the best of my knowledge information and belief at the present time.

Signature		Date	
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EXHIBIT S

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

In Re: TAXOTERE (DOCETAXEL)
PRODUCTS LIABILITY
LITIGATION

MDL NO. 2740

SECTION "H" (5)

THIS DOCUMENT RELATES TO
ALL CASES

THIRD AMENDED PLAINTIFF FACT SHEET

This Fact Sheet must be completed by each plaintiff who has filed a lawsuit related to the use of Taxotere® by the plaintiff or a plaintiff's decedent. Please answer every question to the best of your knowledge. In completing this Fact Sheet, you are under oath and must provide information that is true and correct to the best of your knowledge. If you cannot recall all of the details requested, please provide as much information as you can. You must supplement your responses if you learn that they are incomplete or incorrect in any material respect.

In filling out this form, please use the following definitions: (1) **"healthcare provider"** means any hospital, clinic, medical center, physician's office, infirmary, medical or diagnostic laboratory, or other facility that provides medical, dietary, psychiatric, or psychological care or advice, and any pharmacy, weight loss center, x-ray department, laboratory, physical therapist or physical therapy department, rehabilitation specialist, physician, psychiatrist, osteopath, homeopath, chiropractor, psychologist, nutritionist, dietician, or other persons or entities involved in the evaluation, diagnosis, care, and/or treatment of the plaintiff or plaintiff's decedent; (2) **"document"** means any writing or record of every type that is in your possession, including but not limited to written documents, documents in electronic format, cassettes, videotapes, photographs, charts, computer discs or tapes, and x-rays, drawings, graphs, phone-records, non-identical copies, and other data compilations from which information can be obtained and translated, if necessary, by the respondent through electronic devices into reasonably usable form.

Information provided by plaintiff will only be used for purposes related to this litigation and may be disclosed only as permitted by the protective order in this litigation. This Fact Sheet is completed pursuant to the Federal Rules of Civil Procedure governing discovery (or, for state court case, the governing rules of civil of the state in which the case is pending).

I. CORE CASE INFORMATION

Attorney Information

Please provide the following information for the civil action that you filed:

1. Caption: Hughes v. Accord Healthcare, Inc.
2. Court and Docket No.: 2:17-cv-11769
3. MDL Docket No. (if different): 2740

4. Date Lawsuit Filed: November 3, 2017
5. Plaintiff's Attorney: Samuel M. Wendt
6. Plaintiff's Law Firm: Wendt Law Firm, P.C.
7. Attorney's Address: 1100 Main Street, Suite 2610
Kansas City, MO 64105
8. Attorney's Phone Number: (816) 531-4415
9. Attorney's Email Address: sam@wendtlaw.com

Plaintiff Information

Please provide the following information for the individual on whose behalf this action was filed:

10. Name: HUGHES, ALICE D
11. Street Address: [REDACTED]
12. City: [REDACTED]
13. State: [REDACTED]
14. Zip code: [REDACTED]
15. Date of Birth: [REDACTED]
16. Place of Birth: [REDACTED]
17. Social Security Number: [REDACTED]
18. Maiden or other names you have used or by which you have been known:
Alice Durio
19. Sex: Male: ☐ Female: ☒
20. Race:

Race	Yes
American Indian or Alaska Native	<input type="checkbox"/>
Asian	<input type="checkbox"/>
Black or African American	<input type="checkbox"/>
Native Hawaiian or Other Pacific Islander	<input type="checkbox"/>
White	<input checked="" type="checkbox"/>

21. Ethnicity:

Ethnicity	Yes
Hispanic or Latino	<input type="checkbox"/>
Not Hispanic or Latino	<input checked="" type="checkbox"/>

22. Primary Language: English

Representative Information

If you are completing this questionnaire in a representative capacity (e.g., on behalf of the estate of a deceased person), please state the following:

23. Name:
24. Address:
25. Capacity in which you are representing the individual:
26. If you were appointed as a representative by a court, identify the State, Court and Case Number:
 - a) State:
 - b) Court:
 - c) Case Number:
27. Relationship to the Represented Person:
28. State the date of death of the decedent: --/--/----
29. State the place of death of the decedent:
30. Are you filling this questionnaire out on behalf of an individual who is deceased and on whom an autopsy was performed? Yes ☐ No ☐

If you are completing this questionnaire in a representative capacity, please respond to these questions with respect to the person whose medical treatment involved Taxotere® or Docetaxel.

II. PERSONAL INFORMATION

Relationship Information

Please provide the following information for the civil action that you filed:

1. Are you currently: Married: ☒ Single: ☐ Engaged: ☐
Significant other: ☐ Divorced: ☐ Widowed: ☐ Same sex partner: ☐
2. Have you ever been married? Yes ☒ No ☐
3. If yes, for EACH marriage, state the following:

Spouse's Name	Dates of Marriage	Date Marriage Ended	Nature of Termination
Hughes, Sr., Robert M		--/--/----	Still married

Education

4. For each level of education you completed, please check below:
High School: ☒ Vocational School: ☐
College: AA: ☐ BA/BS: ☒ Masters: ☒ PhD: ☐ M.D.: ☐
Other:

Employment

5. Are you currently employed? Yes ☒ No ☐
6. If yes, state the following:
- a) Current employer name: Quest Diagnostic, Inc.
 - b) Address: 4648 South I-10 Service Road West
Metairie, LA 70001
 - c) Telephone number: (800) 877-7484
 - d) Your position there: Microbiologist, M.T., S.M.
7. Are you making a claim for lost wages or lost earning capacity?
Yes ☐ No ☒
8. Only if you are asserting a wage loss claim, please state the following for EACH employer for the last seven (7) years:

Name of Employer	Address of Employer	Dates of Employment	Annual Gross Income	Your Position
		--/--/---- to --/--/---- <input type="checkbox"/> Present		

9. Have you ever been out of work for more than thirty (30) days for reasons related to your health in the last seven (7) years? Yes ☐ No ☒
10. If yes, please state the following:

Name of Employer	Dates	Health Reason
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

YOU MUST ATTACH TAX RETURNS, EMPLOYMENT AUTHORIZATIONS, AND IDENTIFY THE LOSS OF CONSORTIUM PLAINTIFF'S EMPLOYERS IF CLAIMING LOST WAGES OR LOST EARNING CAPACITY DAMAGES.

Worker's Compensation and Disability Claims

11. Within the last ten (10) years, have you ever filed for workers' compensation, social security, and/or state or federal disability benefits?
Yes ☐ No ☒
12. If yes, then as to EACH application, please state the following:

Year Claim Filed	Court	Nature of Claimed Injury	Period of Disability	Award Amount

Military Service

13. Have you ever served in any branch of the military? Yes ☐ No ☒
14. If yes, state the branch and dates of service:

Branch Name	Dates of Service
	--/--/---- to --/--/---- <input type="checkbox"/> Present

15. If yes, were you discharged for any reason relating to your health (whether physical, psychiatric, or other health condition)? Yes ☐ No ☐
16. If yes, state the condition:

Other Lawsuits

17. Within the last ten (10) years, have you filed a lawsuit, relating to any bodily injury, or made a claim, OTHER THAN the present suit? Yes ☐ No ☒

Computer Use

18. Apart from communications to or from your attorney, have you communicated via email, visited any chat rooms, or publicly posted a comment, message or blog entry on a public internet site regarding your experience with or injuries you attribute to Taxotere®, other chemotherapies, or alopecia/hair loss during the past ten (10) years? You should include all postings on public social network sites including Twitter, Facebook, MySpace, LinkedIn, or “blogs” that address the topics above.
Yes ☐ No ☒
19. If yes, please state the following:

Forum Name	Screen Name or User Handle	Date of Post	Substance of Post
		--/--/----	

20. Are you now or have you ever been a member of an alopecia support group?
Yes ☐ No ☒
- a) If yes, identify the group by name:
- b) When did you join the group?

III. PRODUCT IDENTIFICATION

**I HAVE RECORDS DEMONSTRATING USE OF TAXOTERE ® OR OTHER
DOCETAXEL: Yes ☒ No ☐**

YOU MUST UPLOAD THEM BEFORE YOU SUBMIT THIS FACT SHEET

Taxotere®

1. Were you treated with brand name Taxotere ®? Yes ☐ No ☒ Unknown ☐

Other Docetaxel

2. Were you treated with another Docetaxel or generic Taxotere®? Yes ☒ No ☐
3. If yes, select all that apply:

Name of Drug	Yes
Docetaxel – Sanofi-Aventis U.S. LLC d/b/a Winthrop US	<input type="checkbox"/>
Docetaxel – McKesson Corporation d/b/a McKesson Packaging	<input type="checkbox"/>
Docetaxel – Actavis LLC f/k/a Actavis Inc. / Actavis Pharma, Inc.	<input type="checkbox"/>
Docetaxel – Pfizer Inc.	<input type="checkbox"/>
Docetaxel – Sandoz Inc.	<input type="checkbox"/>
Docetaxel – Accord Healthcare, Inc.	<input checked="" type="checkbox"/>
Docetaxel – Hospira Worldwide, LLC f/k/a Hospira Worldwide, Inc. / Hospira, Inc.	<input type="checkbox"/>
Docefrez – Sun Pharma Global FZE	<input type="checkbox"/>
Docefrez – Sun Pharmaceutical Industries, Inc. f/k/a Caraco Pharmaceutical Laboratories, Ltd.	<input type="checkbox"/>
Docetaxel – Teva Parenteral Medicines, Inc.	<input type="checkbox"/>
Docetaxel – Dr. Reddy’s Laboratories Limited	<input type="checkbox"/>
Docetaxel – Eagle Pharmaceuticals, Inc.	<input type="checkbox"/>
Docetaxel – Northstar Rx LLC	<input type="checkbox"/>
Docetaxel – Sagent Pharmaceuticals, Inc.	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

4. **IF YOU SELECTED “UNKNOWN” YOU MUST CERTIFY AS FOLLOWS:**

I certify that I have made reasonable, good faith efforts to identify the manufacturer of the Docetaxel used in my treatment, including requesting records from my infusion pharmacy, and the manufacturer either remains unknown at this time or I am awaiting the records: ☐

IV. MEDICAL INFORMATION

Vital Statistics

1. How old are you: [REDACTED]

2. Age at the time of your alleged injury: ■
3. Current weight: 117
4. Current height:
Feet: 5 Inches: 6
5. Weight at time of alleged injury: 124

Gynecologic and Obstetric History

6. Have you ever been pregnant? Yes ☒ No ☐
 - a) Number of pregnancies: 02
 - b) Number of live births: 02
7. If you have children, please state the following for EACH child:

Child's Name	Address	Date of Birth
Hughes , Robert M	3536 Ridgeway Metairie , LA 70002	■■■■■
Scorsone , Jennifer	6969 Argonne Blvd. New Orleans , LA 70124	■■■■■

8. Date of first period (menses): ■■■■■ Age: ■■■
9. Date of last period (menses): ■■■■■ Age: ■■■
10. Are you menopausal, perimenopausal or postmenopausal? Yes ☒ No ☐
11. For EACH year for the last seven (7) years before your first treatment with Taxotere® or Docetaxel and since then, who did you see for your annual gynecological exam? Also indicate whether an annual exam was skipped or missed.

Doctor	Office	Year	Skipped or Missed
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2017	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2016	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2015	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2014	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2013	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2012	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2011	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2010	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2009	<input type="checkbox"/>

Doctor	Office	Year	Skipped or Missed
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2008	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2007	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2006	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2005	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2004	<input type="checkbox"/>
Waters, Donna	3434 Prytania St., Suite 320 New Orleans, LA	2018	<input type="checkbox"/>

12. For EACH year after age 40, or before then if applicable, who did you see for your annual mammogram? Also indicate whether an annual mammogram was skipped or missed.

Doctor	Office	Year	Skipped or Missed
Waters , Donna	101 W. Robert E. Lee Blvd. Ste 201 New Orleans, LA 70124	1993	<input type="checkbox"/>
Waters , Donna	101 W. Robert E. Lee Blvd. Ste 201 New Orleans, LA 70124	1994	<input type="checkbox"/>
Waters , Donna	101 W. Robert E. Lee Blvd. Ste 201 New Orleans, LA 70124	1995	<input type="checkbox"/>
Waters , Donna	101 W. Robert E. Lee Blvd. Ste 201 New Orleans, LA 70124	1996	<input type="checkbox"/>
Waters , Donna	101 W. Robert E. Lee Blvd. Ste 201 New Orleans, LA 70124	1997	<input type="checkbox"/>
Waters , Donna	101 W. Robert E. Lee Blvd. Ste 201 New Orleans, LA 70124	1998	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	1999	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2000	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2001	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2002	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2003	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2004	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2005	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2006	<input type="checkbox"/>
Donna	3434 Prytania St., Suite 320 New Orleans, LA	2007	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2008	<input type="checkbox"/>

Doctor	Office	Year	Skipped or Missed
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2009	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2010	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2011	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2012	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2013	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2014	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2015	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2016	<input type="checkbox"/>
Waters , Donna	3434 Prytania St., Suite 320 New Orleans, LA	2017	<input type="checkbox"/>
Waters, Donna	3434 Prytania St., Suite 320 New Orleans, LA	2018	<input type="checkbox"/>

Other Risk Factors

13. Have any family members been diagnosed with breast cancer?

Family Member	Diagnosed	Age at Diagnosis
	<input type="checkbox"/>	

14. Have you ever been diagnosed as having genes or gene mutations that carry an increased cancer risk (e.g., BRCA1, BRCA2)? Yes ☐ No ☒

a) If yes, which?

15. Did you receive radiation treatments or exposure to radiation before the age of 30? Yes ☐ No ☒

a) If yes, describe the particulars of your treatment or exposure:

Tobacco Use History

For the ten (10) year period before your use of Taxotere® or Docetaxel up to the present, check the answer and fill in the blanks applicable to your history of tobacco use, including cigarettes, cigars, pipes, and/or chewing tobacco/snuff.

16. I currently use tobacco: Yes ☐ No ☒

17. I have never used tobacco: Yes ☒ No ☐

18. I used tobacco in the ten (10) years before Taxotere® or Docetaxel treatment:

Yes ☐ No ☒

19. Identify types of tobacco use:

Type	Used	Average Per Day	Duration of Use (Years)
Cigarettes	<input type="checkbox"/>		
Cigars	<input type="checkbox"/>		
Pipes	<input type="checkbox"/>		
Chewing tobacco/snuff	<input type="checkbox"/>		

Prescription Medications

20. Apart from chemotherapy, are there prescription or over-the-counter medications that you took on a regular basis or more than three (3) times in the seven (7) year period before you first took Taxotere®? Yes ☒ No ☐

For purposes of this question, "regular basis" means that you were directed by a healthcare provider to take a medication for at least forty-five (45) consecutive days.

21. If yes, please provide the following for EACH prescription medication:

Medication	Prescriber	Dates Taken
Birth Control - ***can't remember exact brand***	Waters , Donna 3434 Prytania St. New Orleans , LA 70115	??/??/1976 to ??/??/2000 <input type="checkbox"/> Present
HTCZ	Waters, Donna 3434 Prytania Street New Orleans, LA 70115	??/--/2004 to ??/--/2012 <input type="checkbox"/> Present

V. CANCER DIAGNOSIS AND TREATMENT

Cancer Diagnosis & Treatment Generally

1. Have you ever been diagnosed with cancer? Yes ☒ No ☐
2. Were you diagnosed with cancer more than once? Yes ☐ No ☒
3. Did you undergo any of the following for cancer?

Treatment	Treated
Surgery	<input checked="" type="checkbox"/>
Radiation	<input checked="" type="checkbox"/>
Chemotherapy	<input checked="" type="checkbox"/>

4. For surgery, specify:

Type of Surgery	Treated
Double mastectomy	<input type="checkbox"/>
Left-side mastectomy	<input type="checkbox"/>
Right-side mastectomy	<input type="checkbox"/>
Lumpectomy	<input checked="" type="checkbox"/>
Other:	<input type="checkbox"/>

5. Please state the following for EACH cancer diagnosis:

Type of Cancer	Right Breast Cancer
Date of Diagnosis	08/30/2011
Primary Oncologist	09/30/2011 to --/--/---- <input checked="" type="checkbox"/> Present Chemotherapy and Oncology Follow Up Care Veith, M.D., Robert 3800 Houma Blvd. #200 Metairie, LA 70006
Primary Oncologist	01/31/2012 to 05/24/2012 <input type="checkbox"/> Present Radiation Therapy Consult, Treatment and Follow Up Care Monsour, M.D., Paul 4204 Houma Blvd. Metairie, LA 70006
Primary Oncologist	09/2/2011 to 09/13/2011 <input type="checkbox"/> Present Right Breast Surgery Stolier, M.D., Alan 2525 Severn Avenue Metairie, LA 70002
Treatment Facility	08/26/2011 to --/--/---- <input checked="" type="checkbox"/> Present Right Breast Biopsy, Mammograms, Radiology and Labwork East Jefferson General Hospital 4200 Houma Blvd. Metairie, LA 70006
Treatment Facility	01/31/2012 to 05/24/2012 <input type="checkbox"/> Present Radiation Therapy Consult, Therapy and Follow Up Care East Jefferson Radiation Oncology, LLC 4204 Houma Blvd. Metairie, LA 70006
Treatment Facility	09/13/2011 to 09/13/2011 <input type="checkbox"/> Present Right Breast Lumpectomy, Sentinel Lymph Node and Axillary Dissection Omega Hospital 2525 Severn Avenue Metairie, LA 70002
Treatment Facility	--/--/---- to --/--/---- <input type="checkbox"/> Present

Particulars of Chemotherapy

6. When were you first diagnosed with the condition for which you were prescribed Taxotere® or

Docetaxel? 08/30/2011

7. What was the diagnosis for which you were prescribed Taxotere® or Docetaxel?

Diagnosis	Diagnosed
Breast cancer	<input checked="" type="checkbox"/>
Non-small cell lung cancer	<input type="checkbox"/>
Prostate cancer	<input type="checkbox"/>
Gastric adenocarcinoma	<input type="checkbox"/>
Head and neck cancer	<input type="checkbox"/>
Other:	<input type="checkbox"/>

8. For breast cancer, specify:

a) Tumor size:

Tumor Size	Yes
TX	<input type="checkbox"/>
T0	<input type="checkbox"/>
Tis	<input type="checkbox"/>
T1	<input checked="" type="checkbox"/>
T2	<input type="checkbox"/>
T3	<input type="checkbox"/>
T4 (T4a, T4b, T4c, T4d)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

b) Metastasis: No

c) Node involvement:

Node	Yes
Node + NX	<input type="checkbox"/>
Node + N0	<input checked="" type="checkbox"/>
Node + N1	<input type="checkbox"/>
Node + N2	<input type="checkbox"/>
Node + N3	<input type="checkbox"/>
Node – (negative)	<input checked="" type="checkbox"/>
Unknown	<input type="checkbox"/>

d) HER2 + (positive): ☐ HER2- (negative): ☒ Unknown: ☐

e) Estrogen receptor: Positive (ER+): ☒ Negative (ER-): ☐ Unknown: ☐

- f) Progesterone receptor: Positive (PR+): ☐ Negative (PR-): ☒ Unknown: ☐
9. Was Taxotere® or Docetaxel the only chemotherapy treatment that you ever received?
Yes ☐ No ☒ Unknown ☐
10. Have you ever been treated with other chemotherapy drugs, either alone or in combination with or sequentially with Taxotere® or Docetaxel? Yes ☒ No ☐ Unknown ☐
11. If yes, check which of the following chemotherapy drugs you took:

Drug	Yes
5-Fluorouracil (Eludex)	<input type="checkbox"/>
Actinomycin	<input type="checkbox"/>
Altretamine (Hexalen)	<input type="checkbox"/>
Amsacrine	<input type="checkbox"/>
Bleomycin	<input type="checkbox"/>
Busulfan (Busulfex, Myleran)	<input type="checkbox"/>
Cabazitaxel: Mitoxantrone	<input type="checkbox"/>
Carboplatin (Paraplatin)	<input checked="" type="checkbox"/>
Carmustine (BiCNU, Gliadel)	<input type="checkbox"/>
Cetuximab (Erbix)	<input type="checkbox"/>
Chlorambucil (Leukeran)	<input type="checkbox"/>
Cisplatin (Platinol)	<input type="checkbox"/>
Cyclophosphamide (Neosar)	<input type="checkbox"/>
Cytarabine (Depocyt)	<input type="checkbox"/>
Dacarbazine	<input type="checkbox"/>
Daunorubicin (Cerubidine, DaunoXome)	<input type="checkbox"/>
Doxorubicin (Adriamycin, Doxil)	<input type="checkbox"/>
Epirubicin (Ellence)	<input type="checkbox"/>
Erlotinib (Tarceva)	<input type="checkbox"/>
Etoposide (Etopophos, Toposar)	<input type="checkbox"/>
Everolimus (Afinitor, Zortress)	<input type="checkbox"/>
Faslodex (Fulvestrant)	<input type="checkbox"/>
Gemcitabine (Gemzar)	<input type="checkbox"/>
Hexamethylmelamine (Hexalen)	<input type="checkbox"/>
Hydroxyurea (Hydrea, Droxia)	<input type="checkbox"/>
Idarubicin (Idamycin)	<input type="checkbox"/>
Ifosfamide (Ifex)	<input type="checkbox"/>
L-asparaginase (crisantaspase)	<input type="checkbox"/>
Lomustine (Ceenu)	<input type="checkbox"/>
Melphalan (Alkeran)	<input type="checkbox"/>

Drug	Yes
Mercaptopurine (Purinethol, Purixan)	<input type="checkbox"/>
Methotrexate (Trexall, Rasuvo)	<input type="checkbox"/>
Mitomycin	<input type="checkbox"/>
Mitoxantrone	<input type="checkbox"/>
Nab-paclitaxel (Abraxane): Mitoxantrone	<input type="checkbox"/>
Nitrogen mustard	<input type="checkbox"/>
Paclitaxel (Taxol)	<input type="checkbox"/>
Panitumumab (Vectibix)	<input type="checkbox"/>
Procarbazine (Matulane)	<input type="checkbox"/>
Sorafenib (Nexavar)	<input type="checkbox"/>
Teniposide (Vumon)	<input type="checkbox"/>
Thioguanine (Tabloid)	<input type="checkbox"/>
Thiotepa (Tepadina)	<input type="checkbox"/>
Topotecan (Hycamtin)	<input type="checkbox"/>
Vemurafenib (Zelboraf)	<input type="checkbox"/>
Vinblastine	<input type="checkbox"/>
Vincristine (Mariqibo, Vincasar)	<input type="checkbox"/>
Vindesine	<input type="checkbox"/>
Vinorelbine (Alocrest, Navelbine)	<input type="checkbox"/>
Unknown	<input type="checkbox"/>

12. Please provide the following information regarding Taxotere® or Docetaxel:

- a) Number of cycles: 06
- b) Frequency: Every week ☐ Every three weeks ☐
Other: Every 2 weeks
- c) First treatment date: 11/14/2011
- d) Last treatment date: 02/7/2012
- e) Dosage: 80 mg
- (1) Combined with another chemotherapy drug: ☒
- (2) Sequential with another chemotherapy drug: ☐
- (3) If so, describe the combination or sequence: Six cycles of Docetaxel and Carboplatin

13. Prescribing Physician(s):

Prescribing Physician	Address
Veith, M.D., Robert	3800 Houma Blvd. Metairie , LA 70006

14. Treatment Facility:

Treatment Facility	Address
Office of Dr. Robert Veith	3800 Houma Blvd. Metairie , LA 70006

15. Identify EACH state where you resided when you began and while taking Taxotere® or Docetaxel:

State	From Date	To Date
LA	11/14/2011	02/7/2012 <input type="checkbox"/> Present

16. Was your Taxotere® or Docetaxel treatment part of a clinical trial? Yes ☐ No ☒ Unknown ☐

17. If yes, please provide the name and location of the trial site:

- Name of trial site:
- Location of trial site:

VI. CLAIM INFORMATION

Current Status

- Are you currently taking Taxotere® or Docetaxel? Yes ☐ No ☒
- Are you currently cancer-free? Yes ☒ No ☐
- If no, check those that apply to your CURRENT status:

Current Status	Yes
In remission	<input type="checkbox"/>
Currently receiving chemotherapy	<input type="checkbox"/>
Currently receiving radiation therapy	<input type="checkbox"/>
Currently hospitalized for cancer or cancer-related complications	<input type="checkbox"/>
Currently in home health or hospice care for cancer or cancer-related complications	<input type="checkbox"/>
Cancer returned after taking Taxotere® or Docetaxel	<input type="checkbox"/>

- When was the last (most recent) date you consulted with an oncologist: 03/12/2019

Alleged Injury

5. State the injury you allege in this lawsuit and the dates between which you experienced the alleged injury. Check all that apply:

Alleged Injury	Yes	No	From	To
Persistent total alopecia – No hair growth on your head or body after six (6) months of discontinuing Taxotere® or Docetaxel treatment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2012	--/--/---- <input checked="" type="checkbox"/> Present
Persistent alopecia of your head – No hair growth on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment. Hair is present elsewhere on your body	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Hair Loss on Scalp	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Diffuse thinning of hair: partial scalp <input checked="" type="checkbox"/> Top <input type="checkbox"/> Sides <input type="checkbox"/> Back <input checked="" type="checkbox"/> Temples <input type="checkbox"/> Other:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2012	--/--/---- <input checked="" type="checkbox"/> Present
Diffuse thinning of hair: total scalp <input type="checkbox"/> Top <input type="checkbox"/> Sides <input type="checkbox"/> Back <input type="checkbox"/> Temples <input type="checkbox"/> Other:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Significant thinning of the hair on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment – There are visible bald spots on your head no matter how you style your hair	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2012	--/--/---- <input checked="" type="checkbox"/> Present
Moderate thinning of the hair on your head after six (6) months of discontinuing Taxotere® or Docetaxel treatment – There is noticeable hair loss but if you brush or style your hair, the hair loss is less evident	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Small bald area in the hair on your head	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Large bald area in the hair on your head	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Multiple bald spots in the hair on your head	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Change in the texture, thickness or color of your hair after Taxotere® or Docetaxel treatment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2012	--/--/---- <input checked="" type="checkbox"/> Present
Other:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present

Alleged Injury	Yes	No	From	To
Permanent/Persistent Loss of Eyebrows	<input checked="" type="checkbox"/>	<input type="checkbox"/>	08/??/2012	--/--/---- <input checked="" type="checkbox"/> Present
Permanent/Persistent Loss of Eyelashes	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Body Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Genital Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Nasal Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Ear Hair	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present
Permanent/Persistent Loss of Hair in Other Areas Describe:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	--/--/----	--/--/---- <input type="checkbox"/> Present

6. Have you ever received treatment for the injury you allege in this lawsuit?

Yes ☐ No ☒

Name of Treating Physician	Dates of Treatment	Treatments
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

7. Were you diagnosed by a healthcare provider for the injury you allege in this lawsuit?

Yes ☐ No ☒

Name of Diagnosing Physician	Dates of Treatment	Treatments
	--/--/---- to --/--/---- <input type="checkbox"/> Present	

8. Have you discussed with any healthcare provider whether Taxotere® or Docetaxel caused or contributed to your alleged injury?

Yes ☒ No ☐

Name of Physician	Dates of Treatment	Treatments
Veith , Robert W	03/13/2017 to --/--/---- <input type="checkbox"/> Present	No Treatment - only discussion.

Statement Information

9. Were you ever given any written instructions, including any prescriptions, packaging, package inserts, literature, medication guides, or dosing instructions, regarding chemotherapy, Taxotere® or Docetaxel? Yes ☒ No ☐

10. If yes, please describe the documents, if you no longer have them. If you have the documents, please produce them:

Description of Document	I Have the Documents	I Do Not Have the Documents
Patient Education Quick Reference Guide	<input checked="" type="checkbox"/>	<input type="checkbox"/>

11. Were you given any oral instructions from a healthcare provider regarding chemotherapy or your use of Taxotere® or Docetaxel? Yes ☒ No ☐
12. If yes, please identify each healthcare provider who provided the oral instructions:

Name of Healthcare Provider
Veith , Robert

13. Have you ever seen any advertisements (e.g., in magazines or television commercials) for Taxotere® or Docetaxel? Yes ☒ No ☐
14. If yes, identify the advertisement or commercial, and approximately when you saw the advertisement or commercial:

Type of Advertisement or Commercial	Date of Advertisement or Commercial
TV Commercial	??/??/2016

15. Other than through your attorneys, have you had any communication, oral or written, with any of the Defendants or their representatives? Yes ☐ No ☒
16. If yes, please identify:

Date of Communication	Method of Communication	Name of Representative	Substance of Communication
--/--/----			

17. Have you filed a MedWatch Adverse Event Report to the FDA? Yes ☐ No ☒

YOU MUST UPLOAD NOW ANY MEDICAL RECORDS IN YOUR POSSESSION DEMONSTRATING ALLEGED INJURY OR PHOTOGRAPHS SHOWING YOUR HAIR BEFORE AND AFTER TREATMENT WITH TAXOTERE® ALONG WITH THE DATE(S) THE PHOTOGRAPHS WERE TAKEN.

Other Claimed Damages

18. Mental or Emotional Damages: Do you claim that your use of Taxotere® or Docetaxel caused or aggravated any psychiatric or psychological condition? Yes ☐ No ☒
19. If yes, did you seek treatment for the psychiatric or psychological condition? Yes ☐ No ☐

Provider	Date	Condition
	--/------	

20. Medical Expenses: Do you claim that you incurred medical expenses for the alleged injury that you claim was caused by Taxotere® or Docetaxel? Yes ☐ No ☒
21. If yes, list all of your medical expenses, including amounts billed or paid by insurers and other third-party payors, which are related to any alleged injury you claim was caused by Taxotere® or Docetaxel:

Provider	Date	Expense
	--/------	

22. Lost Wages: Do you claim that you lost wages or suffered impairment of earning capacity because of the alleged injury that you claim was caused by Taxotere® or Docetaxel? Yes ☐ No ☒
23. If yes, state the annual gross income you earned for each of the three (3) years before the injury you claim was caused by Taxotere® or Docetaxel.

Year	Annual Gross Income

24. State the annual gross income for every year following the injury or condition you claim was caused by Taxotere® or Docetaxel.

Year	Annual Gross Income

25. Out-of-Pocket Expenses: Are you making a claim for lost out-of-pocket expenses? Yes ☒ No ☐
26. If yes, please identify and itemize all out-of-pocket expenses you have incurred:

Expense	Expense Amount
Wigs (2011- Present)	Approx.\$1,080

VII. HAIR LOSS INFORMATION

Background

1. Did you ever see a healthcare provider for hair loss BEFORE taking Taxotere® or Docetaxel?
Yes ☐ No ☒
2. Did your hair loss begin during chemotherapy treatment? Yes ☒ No ☐
3. If yes, did you FIRST experience hair loss:
 - a) After treatment with another chemotherapy agent: ☐
 - b) After treatment with Taxotere® or Docetaxel: ☒
4. At any time before or during the hair loss were you:

Condition	Yes	Description
Pregnant	<input type="checkbox"/>	
Seriously ill	<input type="checkbox"/>	
Hospitalized	<input type="checkbox"/>	
Under severe stress	<input type="checkbox"/>	
Undergoing treatment for any other medical condition	<input type="checkbox"/>	

5. When did you FIRST discuss with or see a healthcare provider about your hair loss?
03/13/2017
6. Have you started any special diets at any time before or during the hair loss?
Yes ☐ No ☒ Describe:

Hair Loss History

Question	No	Yes	Name of Healthcare Provider
Have you had a biopsy of your scalp to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you had blood tests done to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have your hormones ever been checked to evaluate your hair loss problem?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you ever been told by a doctor that you have a thyroid condition?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you ever been treated with thyroid hormone?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Have you ever been told by a doctor that you have a low iron level?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

7. Have you ever been on endocrine or hormonal therapy, either before or after chemotherapy with Taxotere® or Docetaxel? Yes ☒ No ☐
8. If yes, please identify:

Treating Physician	Dates of Treatment	Treatment
Veith, M.D., Robert	05/1/2012 to --/--/---- <input checked="" type="checkbox"/> Present	Letrozole (Femara)

9. Do you have any autoimmune diseases? Yes ☐ No ☒

10. If yes, check the following which describes you:

Autoimmune Disease	Yes
Lupus	<input type="checkbox"/>
Rheumatoid arthritis	<input type="checkbox"/>
Celiac disease	<input type="checkbox"/>
Type 1 diabetes	<input type="checkbox"/>
Sjogrens disease	<input type="checkbox"/>
Vitiligo	<input type="checkbox"/>
Hashimoto's	<input type="checkbox"/>
Other:	<input type="checkbox"/>

11. Were you taking any medications when your hair loss began? Yes ☒ No ☐

Medication
Carboplatin
Docetaxel
Decadron
Zofran
Neulasta
Hydrochlorothiazide

Hair Care

12. How often do you wash/shampoo your hair? Every 2 days

13. Check any of the following that apply to you currently or that have in the past:

Hair Treatment	Yes	Period of Time	Frequency
Hair chemically processed or straightened (relaxers, keratin, Brazilian blowout, Japanese straightening, other)	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	

Hair Treatment	Yes	Period of Time	Frequency
Hair heat processed or straightened (blow drying/flat ironing, curling)	<input checked="" type="checkbox"/>	??/--/1973 to ??/--/2003 <input type="checkbox"/> Present	2-3 times a week
Hair dyed	<input checked="" type="checkbox"/>	??/--/2003 to ??/--/2011 <input type="checkbox"/> Present	Once every 1-2 months
Hair highlighted	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Braids	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Weaves	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Tight hairstyles (ponytails)	<input checked="" type="checkbox"/>	--/--/1960 to --/--/2003 <input type="checkbox"/> Present	Once a week
Extensions	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	
Other:	<input type="checkbox"/>	--/--/---- to --/--/---- <input type="checkbox"/> Present	

14. Have you ever used the following?

Hair Treatment	Yes
WEN Cleansing Conditioners	<input type="checkbox"/>
Unilever Suave Professionals Keratin Infusion	<input type="checkbox"/>
L'Oréal Chemical Relaxer	<input type="checkbox"/>

15. Has your hair care regimen been different in the past? Yes ☐ No ☒

a) If yes, describe:

Hair Loss Treatment

16. Did you use any other methods to prevent hair loss during chemotherapy?

Hair Treatment	Yes
Folic Acid supplementation	<input type="checkbox"/>
Minoxidil	<input type="checkbox"/>
Other:	<input type="checkbox"/>

17. Did you wear a cool cap during chemotherapy treatment? Yes ☐ No ☒

18. If yes, which cooling cap did you wear:

19. Have you used any over-the-counter medications, supplements, or cosmetic aides for your hair loss? Yes ☐ No ☒

20. If yes, please state the following:

Treatment	When was it tried?	How long did you try it?	Did it help?
	--/--/----		

21. Has anything helped your hair loss? Yes ☐ No ☒

22. If yes, please specify:

Type of Product	Dates of Use	Place of Purchase	Results of Use
	--/--/---- to --/--/---- <input type="checkbox"/> Present		

23. As of the date you verify your PFS, how long have you had alopecia or incomplete hair regrowth? Since August 2012

24. Has any hair regrowth occurred? Yes ☒ No ☐

25. Have you ever worn a wig to conceal your hair loss? Yes ☒ No ☐

26. Specify:

Dates Used	Period of Use	Place Purchased	Cost of Item
12/??/2011 to --/--/---- <input checked="" type="checkbox"/> Present	Every 6 months.	Wig World 8 Wigs purchased	Approx. \$1,080.00

VIII. RECORD HOLDER IDENTIFICATION

Healthcare Providers:

- Identify each physician, doctor, or other healthcare provider who has provided treatment to you for any reason in the past eight (8) years and the reason for consulting the healthcare provider or mental healthcare provider.

YOU MUST INCLUDE YOUR ONCOLOGIST, RADIOLOGIST, DERMATOLOGIST, DERMATOLOGIST-PATHOLOGIST, HAIR LOSS SPECIALIST, GYNECOLOGIST, OBSTETRICIAN, AND PRIMARY CARE PHYSICIAN, ALONG WITH ANY OTHER HEALTHCARE PROVIDERS IDENTIFIED ABOVE

Name	Area or Specialty	Address	Dates	Reason for Consultation
Veith, M.D., Robert	Oncologist	4224 Houma Blvd. Metairie , LA 70006	09/30/2011 to --/--/---- <input checked="" type="checkbox"/> Present	Breast Cancer - Chemotherapy and oncology follow up care.
Waters, M.D., Donna	OBGYN	3434 Prytania St., Suite 320 New Orleans , LA 70115	??/??/1986 to --/--/---- <input checked="" type="checkbox"/> Present	OBGYN - Annual Exams

Name	Area or Specialty	Address	Dates	Reason for Consultation
Monsour, M.D., Paul	Oncologist - Radiation	4204 Houma Blvd. Metairie , LA 70006	01/31/2012 to 05/24/2012 <input type="checkbox"/> Present	Breast Cancer - Radiation therapy and follow up care.
Stolier, M.D., Alan	Surgery	2525 Severn Avenue Metairie, LA 70002	09/2/2011 to 09/13/2011 <input type="checkbox"/> Present	Right breast lumpectomy and follow up care.
Gordon, M.D., John	Surgery	4228 Houma Blvd #220 Metairie, LA 70006	02/21/2013 to 02/21/2013 <input type="checkbox"/> Present	Left Breast biopsy and aspiration of cyst.
Bopp, M.D., Barbara	Dermatology	3421 N. Causeway, Ste 102 Metairie, LA 70006	07/9/2018 to 07/9/2018 <input type="checkbox"/> Present	Skin assessment for moles, actinic keratosis.
Karlin, M.D., Richard	Surgery	3901 Houma Blvd #400 Metairie, LA 70006	10/30/2017 to 10/30/2017 <input type="checkbox"/> Present	Laparoscopic Left Inguinal Herniorrhaphy
Jeanfreau, M.D., Wallace	Internal Medicine	3625 Houma Blvd Metairie, LA 70006	--/--/?? to --/--/?? <input type="checkbox"/> Present	Primary Care physician. Records requested, dates currently unknown.

Hospitals, Clinics, and Other Facilities:

- Identify each hospital, clinic, surgery center, physical therapy or rehabilitation center, or other healthcare facility where you have received inpatient or outpatient treatment (including emergency room treatment) in the past eight(8)years:

YOU MUST INCLUDE THE LOCATIONS FOR SURGERIES, RADIOLOGY, IMAGING, BIOPSIES, CHEMOTHERAPY, CHILD BIRTHS, GYNECOLOGIC PROCEDURES OR TREATMENT, ALONG WITH ANY OTHER HEALTHCARE FACILITIES

Name	Address	Dates	Reason for Treatment
Omega Hospital	2525 Severn Ave. Metairie , LA 70002	09/13/2011 to 09/13/2011 <input type="checkbox"/> Present	Right breast lumpectomy.
Office of Dr. Veith	3800 Houma Blvd. Metairie , LA 70002	09/30/2011 to --/--/---- <input checked="" type="checkbox"/> Present	Chemotherapy and Oncology follow up care.
Office Dr. Waters	3434 Prytania St. Ste 320 New Orleans, LA 70006	??/??/1986 to --/--/---- <input checked="" type="checkbox"/> Present	OBGYN
East Jefferson Radiation Oncology	4204 Houma Blvd. Metairie , LA 70006	01/31/2012 to 05/24/2012 <input type="checkbox"/> Present	Radiation therapy for breast cancer.
East Jefferson General Hospital	4200 Houma Blvd Metairie, LA 70006	07/14/2004 to --/--/---- <input checked="" type="checkbox"/> Present	Mammograms, Ultrasounds, Bone Scans, Radiology, Labwork, Hospitalizations.

Laboratories:

3. Identify each laboratory at which you had tests run in the past ten (10) years:

Name	Address	Dates	Test	Reason for Tests
East Jefferson General Pathology Lab	4200 Houma Blvd. Metairie , LA 70006	08/??/2007 to --/--/---- <input checked="" type="checkbox"/> Present	CBC, CMP	Follow up after chemotherapy.
Quest Diagnostics	4200 Houma Blvd. Metairie , LA 70006	09/??/2011 to --/--/---- <input checked="" type="checkbox"/> Present	CBC, CMP	Follow up after chemotherapy.

Pharmacies:

4. To the best of your recollection, Identify each pharmacy, drugstore, and/or other supplier (including mail order) where you have had prescriptions filled or from which you have ever received any prescription medication within three (3) years prior to and three (3) years after your first treatment with Taxotere:

Name	Address	Dates	Medications
Rite Aid	4300 W. Esplanade Ave. Metairie , LA 70006	09/??/2011 to 06/??/2017 <input type="checkbox"/> Present	Letrozole
CVS	4950 W. Esplanade Ave. Metairie , LA 70006	07/??/2017 to --/--/---- <input checked="" type="checkbox"/> Present	Letrozole

Retailers:

5. Identify each pharmacy, drugstore, and/or other retailer (including mail order) where you have purchased over-the-counter medications, or hair products in the past ten (10) years:

Name	Address	Dates	Purchases
Rite Aid	4300 W. Esplanade Ave. Metairie , LA 70006	01/??/2007 to 09/??/2011 <input type="checkbox"/> Present	Shampoo Hair Dye
CVS	4950 W. Esplanade Ave. Metairie , LA 70006	07/??/2017 to --/--/---- <input checked="" type="checkbox"/> Present	OC medication & various toiletries
Breaux Mart Grocery	2904 Severne Ave. Metairie , LA 70002	??/??/2008 to ??/??/2012 <input type="checkbox"/> Present	Shampoo Conditioner
Mela Luca Wellness Company	5301 N. National Dr. Knoxville , TN 37914	??/??/2012 to --/--/---- <input checked="" type="checkbox"/> Present	Shampoo

Insurance Carriers:

6. Identify each health insurance carrier which provided you with medical coverage and/or pharmacy benefits for the last ten (10) years:

Carrier	Address	Name of Insured & SSN	Policy Number	Dates of Coverage
Benefit Management Services (BCBS)	PO Box 98044 Baton Rouge , LA 70898	Hughes , Robert	██████	??/??/1980 to --/--/---- <input checked="" type="checkbox"/> Present

IX. DOCUMENT REQUESTS AND AUTHORIZATIONS

Please state which of the following documents you have in your possession. If you do not have the following documents but know they exist in the possession of others, state who has possession of the documents: Produce all documents in your possession (including writings on paper or in electronic form) and signed authorizations and attach a copy of them to this PFS.

Requests

Type of Document(s)	Yes	No	If No, who has the document(s)?
Documents you reviewed to prepare your answers to this Plaintiff Fact Sheet. <i>Your attorney may withhold some documents on claims of attorney-client privilege or work product protection and, if so, provide a privilege log</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Medical records or other documents related to the use of Taxotere® or Docetaxel at any time for the past twelve (12) years.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Medical records or other documents related to your treatment for any disease, condition or symptom referenced above for any time in the past twelve (12) years.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Laboratory reports and results of blood tests performed on you related to your hair loss.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA
Pathology reports and results of biopsies performed on you related to your hair loss. <i>Plaintiffs or their counsel must maintain the slides and/or specimens requested in this subpart, or send a preservation notice, copying Defendants, to the healthcare facility where these items are maintained.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Documents reflecting your use of any prescription drug or medication at any time within the past eight (8) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Rite Aid & CVS
Documents identifying all chemotherapy agents that you have taken.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Documents for any workers' compensation, social security or other disability proceeding at any time within the last five (5) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA
Instructions, product warnings, package inserts, handouts or other materials that you were provided or obtained in connection with your use of Taxotere®.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Type of Document(s)	Yes	No	If No, who has the document(s)?
Advertisements or promotions for Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA
Articles discussing Taxotere®.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA
Any packaging, container, box, or label for Taxotere® or Docetaxel that you were provided or obtained in connection with your use of Taxotere®. <i>Plaintiffs or their counsel must maintain the originals of these items.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA
Documents which mention Taxotere® or Docetaxel or any alleged health risks related to Taxotere®. <i>Your attorney may withhold some legal documents, documents provided by your attorney, or documents obtained or created for the purpose of seeking legal advice or assistance on claims of attorney-client privilege or work product protection and, if so, provide a privilege log.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Documents obtained directly or indirectly from any of the Defendants.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Unknown
Communications or correspondence between you and any representative of the Defendants.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Unknown
Photographs, drawing, slides, videos, recordings, DVDs, or any other media that show your alleged injury or its effect in your life.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Journals or diaries related to the use of Taxotere® or Docetaxel or your treatment for any disease, condition or symptom referenced above at any time for the past twelve (12) years.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA
Social media or internet posts to or through any site (including, but not limited to, Facebook, MySpace, LinkedIn, Google Plus, Windows Live, YouTube, Twitter, Instagram, Pinterest, blogs, and Internet chat rooms/message boards) relating to Taxotere® or Docetaxel or any of your claims in this lawsuit.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA
If you claim you have suffered a loss of earnings or earning capacity, your federal tax returns for each of the five (5) years preceding the injury you allege to be caused by Taxotere® or Docetaxel, and every year thereafter or W-2s for each of the five (5) years preceding the injury you allege to be caused by Taxotere® or Docetaxel, and every year thereafter.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA
If you claim any medical expenses, bills from any physician, hospital, pharmacy or other healthcare providers.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA
Records of any other expenses allegedly incurred as a result of your alleged injury.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Unknown
If you are suing in a representative capacity, letters testamentary or letters of administration.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA

Type of Document(s)	Yes	No	If No, who has the document(s)?
If you are suing in a representative capacity on behalf of a deceased person, decedent's death certificate and/or autopsy report.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NA
Photographs of you that are representative of your hair composition before treatment with Taxotere® or Docetaxel.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Photographs of you that are representative of your hair composition during treatment with Taxotere® or Docetaxel.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Photographs of you that are representative of your hair composition six months after conclusion of treatment with Taxotere® or Docetaxel.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Unknown
Photographs of you that are representative of your hair composition in present day.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Signed authorizations for medical records related to any cancer treatment identified herein and all pharmacy records from three (3) years before and three (3) years after your first treatment with Taxotere in the forms attached hereto.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

X. DECLARATION

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that all of the information provided in connection with this Plaintiff Profile Form is true and correct to the best of my knowledge information and belief at the present time.

Signature		Date	
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EXHIBIT T

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL)
PRODUCTS LIABILITY
LITIGATION

Docket No.: 16-MD-2740
Section "H(5)"
September 16, 2019
New Orleans, Louisiana

Relates To: Barbara Earnest,
Case No.: 16-CV-17144

* * * * *

DAY 1, MORNING SESSION
TRANSCRIPT OF JURY TRIAL PROCEEDINGS
HEARD BEFORE THE HONORABLE JANE TRICHE MILAZZO
UNITED STATES DISTRICT JUDGE

APPEARANCES:

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1 back and something that can be disfiguring for a lifetime.

2 Just think if there is a -- my grandkids, you know,
3 the tattoos -- if my grandkids had, you know, one of those --

4 MR. STRONGMAN: Objection, outside of the scope of the
5 question.

6 THE COURT: Sustained. Let's proceed. I think the
7 question was, if they're different, please explain that.

8 THE WITNESS: They are very different. Just think if
9 you're a patient and I'm going to give you a drug and it's an
10 important drug, there are other drugs that also can be given,
11 and that's going to -- I'm going to say, you know, you're going
12 to have hair loss and it's going to grow back in, you know,
13 three months or six months. You'll say, hey, I'm not going to
14 like that, but I'll probably endure that.

15 If I know that it's -- or there is a chance that
16 it's going to be permanent, it's never going to grow back, that
17 would be information that you would want.

18 EXAMINATION BY MR. NOLEN:

19 Q. And, Doctor, just to crystalize that --

20 THE COURT: Was there an objection?

21 MR. STRONGMAN: Go ahead. He finished.

22 THE COURT: Okay.

23 EXAMINATION BY MR. NOLEN:

24 Q. Just to crystalize that, Doctor, alopecia is the issue,
25 right? That's the issue we're here about, permanent alopecia

DAVID KESSLER CROSS

2:12PM 1 BY MR. STRONGMAN:

2:12PM 2 Q. Ready to proceed?

2:12PM 3 A. I am.

2:12PM 4 Q. Very good. So, Doctor, you can agree with me that your

2:12PM 5 definition of "irreversible alopecia" is in the medical

2:12PM 6 literature, it was generally defined as six months with

2:12PM 7 complete loss of growth or partial regrowth; correct?

2:12PM 8 A. I said the medical literature has generally defined it,

2:12PM 9 right, but do note some exceptions to that.

2:12PM 10 Q. Very good. So there are there are several other

2:12PM 11 definitions in the literature as well; correct?

2:12PM 12 A. Fair. Certainly within Sanofi, et cetera. And different

2:13PM 13 doctors, different publications have different definitions.

2:13PM 14 Q. And, for example, we've seen definitions that go out to

2:13PM 15 12 months or 24 months, things like that; correct?

2:13PM 16 A. Correct.

2:13PM 17 Q. Okay. But you would agree with me that, most of the time

2:13PM 18 in the literature, it's six months. That's the most common?

2:13PM 19 A. I think that's a reasonable period of time. There's no

2:13PM 20 there's no magic to these numbers.

2:13PM 21 Q. Okay. And what we saw also in the literature is I

2:13PM 22 doubt you saw any definition for what you're calling

2:13PM 23 irreversible alopecia as being less than six months?

2:13PM 24 A. I think that would be correct because, in general, you

2:13PM 25 know, before 2000, it was always expected, you know, that hair

OFFICIAL TRANSCRIPT

1 familiar with how Sanofi recorded data?

2 A. Sure.

3 Q. Is that represented in their final clinical study trial
4 data, that locked set that you were talking about?

5 A. Yes.

6 Q. How many patients did Sanofi record in the final
7 clinical study data, the locked data, with ongoing persistent
8 or permanent alopecia as of the end of the ten-year followup in
9 TAX316?

10 A. So in 316, on the T arm, the Taxotere arm, there are
11 29 patients in there who had -- they refer to it in their
12 documents as *ongoing alopecia*. So that was -- yeah, at the end
13 of the study.

14 Q. Were you able to reproduce those numbers when you ran
15 analyses based upon how Sanofi did them as well?

16 A. Yes, I can absolutely reproduce the numbers in their
17 clinical study report.

18 Q. Were you able to verify the length of followup for these
19 patients with ongoing persist permanent hair loss?

20 A. Yes.

21 Q. How many of those patients were represented in the final
22 clinical study data as having followup less than six months?

23 A. So of the 29 patients with ongoing hair loss at the end of
24 the study, of the 29 one of those patients had a followup of
25 less than six months. It was 117 days for one patient.

11:00:27 1 and miniaturized.

11:00:28 2 Q. And, Doctor, we're looking at a picture. Is this picture
11:00:33 3 from the medical literature?

11:00:35 4 A. Yes. This is a picture from a paper that has been
11:00:38 5 published. This is the clinical picture showing the
11:00:42 6 presentation of this condition.

11:00:45 7 Q. And if you could take us through what the indications are
11:00:54 8 that support a diagnosis of permanent chemotherapy-induced
11:00:59 9 alopecia, please.

11:01:02 10 A. The classical diagnosis depends on history that is
11:01:09 11 incomplete hair regrowth six months after the end of
11:01:14 12 chemotherapy. And this is Type 2, because there are only two
11:01:19 13 severity grade, unfortunately, because this is what -- the way
11:01:25 14 we grade the severity is just Type 1 and Type 2.

11:01:29 15 So, this is the severe type, which is called *Type 2*,
11:01:34 16 when you have almost -- you know, involvement of almost the
11:01:38 17 whole scalp with thinning. Severe, severe thinning. And
11:01:45 18 involvement of eyebrows and eyelashes is also very typical.

11:01:50 19 Q. Explain that to the jury, if you would, eyebrows and
11:01:54 20 eyelashes.

11:01:54 21 A. Eyebrows and eyelashes are lost as well. Become very
11:01:59 22 thin.

11:01:59 23 Q. And with a presentation of permanent chemotherapy-induced
11:02:03 24 alopecia, what is the result of a pull test?

11:02:07 25 A. A pull test is usually negative because they have no hair

09:02:01 1 with regard to Dr. Kopreski's analysis in his deposition on page
09:02:07 2 122 of Dr. Glaspy's deposition, the question is: "Okay. Did you
09:02:13 3 have a direct role in the review that was taken that's shown in
09:02:18 4 Figure A?"

09:02:20 5 Objection to the form.

09:02:21 6 And then the answer, "I did not have a role in forming
09:02:25 7 the table or writing the table, planning the table, or suggesting
09:02:31 8 that the table be made." That's talking about Figure A in
09:02:37 9 Dr. Kopreski's reanalysis, which is at the heart of this issue.

09:02:41 10 In Dr. Glaspy's deposition on page 123, the question was
09:02:50 11 stated: "QUESTION: You cannot verify, then, that the material
09:02:54 12 contained in Figure A is accurate or complete?"

09:03:00 13 There was an objection. And then: "ANSWER: I -- not
09:03:05 14 independently. I -- I can only comment assuming these are the
09:03:10 15 data, this is my conclusion. That's all I can do."

09:03:16 16 It's very clear that Dr. Glaspy, the defendant's expert,
09:03:21 17 who intends to rely on the Kopreski reanalysis and testimony, did
09:03:26 18 not independently review that analysis and had nothing to do with
09:03:31 19 putting together any of the tables as he testified.

09:03:34 20 In addition, your Honor, to be clear, the defendant's
09:03:39 21 witness, Dr. Kopreski, is an employee of Sanofi. He is not an
09:03:43 22 expert. He has not been qualified as an expert. He did a post hoc
09:03:48 23 analysis of data that Sanofi's lawyers pulled and put in front of
09:03:53 24 him. It is not an expert report. It's not an expert opinion, and
09:03:57 25 certainly not an expert analysis. Yet, this morning the defendants

09:04:02 1 will be playing the videotaped deposition of Dr. Kopreski
09:04:06 2 explaining his analysis, and that is highly prejudicial to the
09:04:13 3 defendant -- to the plaintiffs, excuse me. It's highly prejudicial
09:04:17 4 to the plaintiffs because the defendants are allowed to present
09:04:19 5 testimony from a non-expert about a post hoc analysis, and they
09:04:25 6 will not have an expert who has independently reviewed and relied
09:04:29 7 on that information.

09:04:30 8 So we would ask that Dr. Kopreski's testimony be stricken
09:04:35 9 and not be allowed to be played for this jury, and that Dr. Glaspy
09:04:40 10 not be permitted in any way to rely on that analysis in his
09:04:44 11 opinions. Thank you.

09:04:46 12 THE COURT: Thank you. Okay. Are we ready to bring in
09:04:51 13 the jury? Okay. Please bring the jury in.

09:05:15 14 Did y'all want to respond?

09:05:17 15 MS. SASTRE: I'm sorry?

09:05:18 16 THE COURT: I thought -- the fevered conversation.

09:05:23 17 MR. STRONGMAN: No, I think your Honor has already ruled
09:05:26 18 on this. Just based on all of the reasons and arguments previously
09:05:30 19 made. Sorry about that.

09:05:30 20 MS. SASTRE: Sorry, your Honor.

09:05:53 21 (WHEREUPON, THE JURY ENTERED THE COURTROOM.)

09:05:53 22 THE COURT: All jurors are present. Court's back in
09:05:53 23 session. You may be seated.

09:05:55 24 Good morning. I apologize that we're a little late
09:05:58 25 getting started today. We're just -- the lawyers and I have been

EXHIBIT U

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF LOUISIANA

IN RE: TAXOTERE (DOCETAXEL)
PRODUCTS LIABILITY LITIGATION

Docket No. 16-MD-2740
Section "N"
New Orleans, Louisiana
Friday, October 27, 2017

[THIS DOCUMENT RELATES TO:
ALL CASES]

TRANSCRIPT OF GENERAL STATUS CONFERENCE
HEARD BEFORE THE HONORABLE KURT D. ENGELHARDT
UNITED STATES DISTRICT JUDGE

APPEARANCES:

FOR THE PLAINTIFFS:

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10:57:03 1 Section No. 15 - Motion Practice. There are a number of
10:57:08 2 motions pending and this section outlines all of them. I will
10:57:14 3 briefly touch on each.

10:57:17 4 Sanofi has filed a motion to dismiss claims barred by the
10:57:21 5 applicable statute of limitations, that is Record Document No. 494.
10:57:29 6 In the steering committee meetings you indicated that there was,
10:57:33 7 would be dismissed at this time.

10:57:34 8 THE COURT: The motion was denied without prejudice
10:57:37 9 yesterday and the order will speak for itself. The Court, without
10:57:43 10 discounting any of the arguments made by the defendants, felt it
10:57:48 11 would be more prudent to take the issues up after the first round
10:57:51 12 of discovery, I should say the first round of bellwether plaintiffs
10:57:57 13 set for that first trial date, where we can look at some
10:58:01 14 particularities among those plaintiffs. I just didn't feel
10:58:05 15 comfortable at this juncture of ruling on it in an in-globo
10:58:09 16 fashion, which I think is what the motion sought from the Court.
10:58:12 17 So I denied it without prejudice, but it's something that we'll
10:58:16 18 certainly revisit.

10:58:18 19 MR. LAMBERT: Thank you, your Honor.

10:58:19 20 And on October 3rd defendants filed a motion for entry of
10:58:23 21 a case substitution protocol, that motion is Record Document 888,
10:58:30 22 and it is fully briefed and submitted to your Honor for ruling.

10:58:34 23 THE COURT: Right.

10:58:35 24 MR. LAMBERT: Likewise, the motion to permit written
10:58:40 25 discovery on the trial pool plaintiffs, that's Record Document